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(54) Title: COMPOSITIONS OF CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AND RADIATION FOR INHIBITION OR PREVENTION OF CARDIOVASCULAR DISEAS

(57) Abstract: A method is provided for the prevention or inhibition of cardiovascular disease comprising the adminiministration of a cyclooxygenase-2 selective inhibitor with a dose of radiation.

COMPOSITIONS OF CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AND RADIATION FOR INHIBITION OR PREVENTION OF CARDIOVASCULAR DISEASE

Cross Reference to Related Application

This application claims priority from Provisional Application Serial No. 60/294,077 filed on May 29, 2001, which is hereby incorporated by reference in its entirety

Field of the Invention

The present invention provides a method for the treatment or prevention of cardiovascular disease. More particularly, the invention is directed toward a method for the treatment or prevention of restenosis.

Background of the Invention

Cardiovascular disease is the number one cause of mortality in the world. Many cardiac disorders (e.g., coronary artery disease [CAD], systemic hypertension, bicuspid aortic valve, hypertrophic cardiomyopathy, mitral valve prolapse) have a heritable basis. Although the precise pathogenesis of CAD is unclear, the risk factors are well known: high blood levels of low density lipoprotein cholesterol (LDL-C) and lipoprotein a, low blood levels of high density lipoprotein cholesterol (HDL-C) and serum vitamin E, and poor physical fitness. High blood levels of triglycerides and insulin reflecting insulin resistance may be risk factors, but the data are less clear. CAD risk is increased by tobacco use; diets high in fat and calories and low in phytochemicals (found in fruits and vegetables), fiber, and vitamins E and C, or diets with relatively low levels of omega-3 polyunsaturated fatty acids (PUFAs); poor stress management; and inactivity. Several systemic diseases (e.g., hypertension, diabetes, hypothyroidism) are also associated with increased CAD risk.

Iscehmic heart disease due to coronary artery stenosis is a significant cause of morbidity and mortality in the United States. Reversal and control of coronary artery disease was originally accomplished through the use of coronary artery bypass graft (CABG) techniques developed in the 1960s. In the 1970s and 1980s, an additional treatment method became available with the development of percutaneous transluminal coronary angioplasty (PTCA). Over 400,000 angioplasties are now performed each year in the United States alone.

Although successful in treating coronary artery disease, a recurring problem with angioplasty has been the occurrence of restenosis. Restenosis has been called the "Achilles' heel" of PTCA. Studies have shown that without intervention, 30%-60% of angioplasties will restenose. The mechanism contributing to restenosis after PTCA include 1) elastic recoil; 2) mural thrombosis with thrombus organization; 3) smooth muscle cell migration, proliferation, and synthesis of extracellular matrix; and 4) late vessel cross-sectional constriction or shrinkage (negative remodeling).

The first component, recoil and remodeling, involves the mechanical collapse and constriction of the treated vessel and does not seem to progress much beyond the first day of treatment. The second component, thrombosis, involves a complex interaction among many hemostatic factors that are triggered following vascular injury. This component has been implicated as a major early mechanism underlying restenosis. The third component involves intimal hyperplasia, which is the proliferative response to injury and consists largely of smooth muscle cell and matrix formation. This process begins within a few days after vessel injury and continues for weeks to months until equilibrium between the vessel wall and lumen is achieved. When excessive, intimal hyperplasia can result in severe luminal renarrowing. The fourth component, negative remodeling, appears to be analogous to wound contracture and may be related to contraction of the periadventitual fibroelastic scar.

The rate of restenosis dropped significantly with the development in the 1990s of endovascular stenting techniques, which addressed the problem of mechanical collapse and contraction. The use of stents has been shown to decrease the incidence of restenosis by approximately 30%. Stents, however, do not address the problem of intimal hyperplasia and may even exacerbate the problem by causing local inflammation and damage to the intimal wall or myointimal junction. Restenosis is especially a problem in situations involving small vessels, ostial lesions, complex long and bifurcating lesions, vein grafts, and diffuse in-stent restenosis.

Recently the local application of radiation or brachytherapy has been used to prevent restenosis. The use of radiation to prevent restenosis is derived from the concept that restenosis is a proliferative wound healing process and proliferating cells are sensitive to low dose radiation. It is well known in the art that ionizing radiation is a potent anti-proliferative agent for both malignant and benign disorders and the use of radiation to modify the wound healing response has been well documented.

Radiation can be delivered over a sustained period using implantable devices such as stents containing radioactive isotopes or can be delivered transiently by insertion of a radioactive device at the site of angioplasty for a time sufficient to provide an anti-proliferative dose of radiation. Numerous implantable devices to prevent restenosis are known in the art. Examples include U.S. Patents 5,871,437 and 6,159,142 that disclose a stent coated with a biodegradable coating containing a radioactive source; U.S. Patent 5,919,126, which discloses a stent coated with a radiopaque material containing a beta-emitting radioisotope; U.S. Patent 6,179,789, which discloses a stent coated with a biocompatible material having a radioactive material dispersed therein; U.S. Patent 6,187,037, which discloses a metal stent containing stable radioactive isotopes with a half-life of less than two months; U.S. Patent 6,196,963, which discloses a temporarily implantable brachytherapy device; and U.S. Patent 6,210,313, which discloses an implantable device coated with a chelator selected for its bonding affinity to a particular radioisotope.

Transient administration of anti-proliferative radiation is typically accomplished by insertion into the coronary artery of a catheter, ribbon or other such device for a time adequate to deliver a dose of radiation sufficient to prevent intimal hyperplasia. Examples of devices for the transient delivery of radiation include U.S. Patent 5,662,580; U.S. Patent 6,196,996; and U.S. Patent 6,200,256.

Although the previously discussed examples have involved the use of beta or gamma radiation, ultraviolet ("UV") radiation can also be used. Examples of the application of UV radiation include U.S. Patent 5,053,033; U.S. Patent 5,116,864; U.S. Patent 5,620,438; and U.S. Patent 6,200,307.

Restenosis is also thought to involve an inflammatory component. Damage to the arterial wall during arterial procedures such as angioplasty and arterial grafting, leads to the release of proinflammatory compounds such as cytokines from macrophages. It has been hypothesized that the ability of radiation to prevent restenosis is due, in part, to the effect of the radiation on inflammatory cells. For example, Rubin et al., (*Intl. J. Radiat. Oncol. Biol. Phys.*, 40:929-941, 1998) reported a reduction in monocytes and adventitial macrophages after irradiation of balloon injured rat carotids, corresponding to decreased intimal hyperplasia.

Because of the inflammatory component of restenosis, several anti-inflammatories have been used. For example, Rab et al. (*J. Am Coll. Cardiol.*, 18:1524-

1528, 1991) administered glucocorticoids with or without colchicine to patients receiving stents and reported an increase in the incidence of coronary artery aneurysms. Valero et al. (*J. Cardiovasc. Pharmacol.*, 31:513-519, 1998), introduced hydrocortisone-loaded microspheres into the arterial walls of rabbits during angioplasty. They reported that hydrocortisone-loaded microspheres were associated with a significant reduction in intimal hyperplasia. Strecker et al. (*Cardiovasc. Intervent. Radiol.*, 21:487-496, 1998), reported that dexamethasone-coated stents showed reduced neointimal hyperplasia in dogs when compared to non-coated stents. In contrast, Lee et al. (*Am. Heart J.*, 138:304, 1999), reported that single dose pretreatment with intravenous methylpridnisolone before coronary stenting had no effect on the change in minimal lumen diameter at 6 months.

Non-steroidal anti inflammatories have also been used to decrease restenosis. Chaldakov (*Med. Hypotheses*, 37:74-75, 1992) proposed the use of the anti-inflammatories sulfasalazine, griseofulvin and colchicine to lessen coronary restenosis after angioplasty. Huang et al. (*Eur. J. Pharmacol.*, 221:381-384, 1992), reported that curcumin, an anti-inflammatory agent from *Curcuma longa*, reduced proliferation of vascular smooth muscle cells *in vitro*. Ishiwata et al. (*J. Am. Coll. Cardiol.* 35:1331-1337, 2000) reported that orally administered N-(3,4-dimethoxycinnamoyl) anthranilic acid (tranilast) resulted in a lower rate of restenosis in stent implanted pig arteries. In contrast, Grinstead et al. (*Coron. Artery Dis.* 4:277-281, 1993) found that oral administration of aniprilose hydrochloride, a synthetic carbohydrate with anti-inflammatory and antiproliferative properties did not prevent coronary intimal proliferation in the swine model of restenosis. None of these references disclose or suggest the use of radiation in combination with anti-inflammatories to prevent restenosis.

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of anti-inflammatory drug discovery. However, common non-steroidal anti-inflammatory drugs (NSAID's) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAID's can produce severe side effects, including life-threatening ulcers that limit their therapeutic potential. An alternative to NSAID's is the use of corticosteroids, which also produce severe adverse effects,

especially when long-term therapy is involved and whose usefulness in preventing restenosis has been questioned (Kong, *Am. Heart J.*, 138:3-4, 1999).

NSAID's have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 " or "prostaglandin G/H synthase II") provides a viable target of inhibition, which more effectively reduces inflammation and produces fewer and less drastic side effects.

Compounds that selectively inhibit cyclooxygenase-2 have been described in U.S. patents 5,380,738; 5,344,991; 5,393,790; 5,434,178; 5,474,995; 5, 510,368 and WO documents WO96/06840, WO96/03388, WO96/03387, WO96/19469, WO96/25405, WO95/15316, WO94/15932, WO94/27980, WO95/00501, WO94/13635, WO94/20480, and WO94/26731.

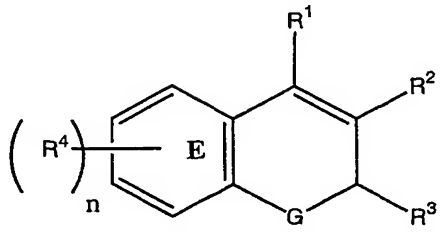
[Pyrazol-1-yl]benzenesulfonamides have been described as inhibitors of cyclooxygenase-2 and have shown promise in the treatment of inflammation, arthritis, and pain, with minimal side effects in pre-clinical and clinical trials. Their use for treating inflammation in vascular disease has been described in U.S. Patent No. 5,466,823. Their use for preventing cardiovascular-related diseases has been described in co-pending U.S. application 09/402,634.

The present inventive discovery is directed to the use of selective inhibitors of cyclooxygenase-2 in combination with radiation for the prevention of restenosis (intimal hyperplasia) following vascular intravention. More specifically, this inventive discovery relates to the use of cyclooxygenase-2 selective inhibitors or derivatives or pharmaceutically acceptable salts or prodrugs thereof in combination with radiation for preventing restenosis following coronary artery intervention.

Summary of the Invention

Among the several aspects of the invention is provided a method for the inhibition or prevention of cardiovascular disease in a subject comprising, the method comprising administering to the subject a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof and a dose of radiation.

In one embodiment, the cyclooxygenase-2 selective inhibitor comprises a compound of the formula:



(I)

wherein n is an integer which is 0, 1, 2, 3 or 4;

wherein G is O, S or NR^a;

wherein R^a is alkyl;

wherein R^1 is selected from the group consisting of H and aryl;

wherein R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

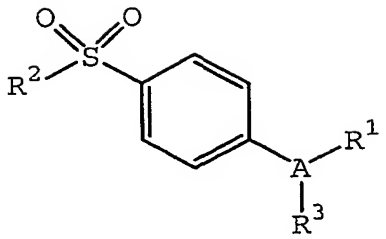
wherein R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical;

or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another embodiment, the cyclooxygenase-2 selective inhibitor or pharmaceutically acceptable salt or prodrug thereof comprises a compound of the formula:



wherein A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R^1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

wherein R^2 is selected from the group consisting of methyl or amino; and

wherein R^3 is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl.

In yet another embodiment, the cell proliferation preventing or inhibiting radiation comprises alpha particles, beta particles, gamma rays, X-rays, ultra violet rays, or any combination of the proceeding.

In another embodiment the dose of cell proliferation preventing or inhibiting radiation is between about 3 Gray and about 60 Gray.

In a further embodiment, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is administered during a continuous period beginning prior to administration of the radiation and ending after administration of the radiation.

In still a further embodiment, the cyclooxygenase-2 selective inhibitor or pharmaceutically acceptable salt or prodrug thereof is administered during a continuous period beginning on the same day as the beginning of the radiation therapy and extending to a period after the end of the radiation therapy.

Abbreviations and Definitions

The term "prevention" includes either preventing the onset of clinically evident restenosis altogether or preventing the onset of a preclinically evident stage of restenosis in individuals. This definition includes prophylactic treatment.

The term "inhibition" as used herein means to prevent or decrease the severity of restenosis as compared to that which would occur in the absence of the application of the method of the present invention.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent which will achieve the goal of improvement in disorder severity and the frequency of incidence over no treatment or treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

The phrase "cell proliferation inhibiting" means an amount that causes or results in a rate of cell proliferation that is less than that which would have occurred in the absence of the application of the present method.

The term "subject" for purposes of treatment includes any human or animal subject who is susceptible to intimal hyperplasia or restenosis. The subject can be a domestic livestock species, a laboratory animal species, a zoo animal or a companion animal. In one embodiment, the subject is a human being.

The term "cyclooxygenase-2 selective inhibitor" denotes a compound able to inhibit cyclooxygenase-2 without significant inhibition of cyclooxygenase-1. Preferably, it includes compounds that have a cyclooxygenase-2 IC_{50} of less than about 0.2 micro molar, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even

more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 micro molar, and more preferably of greater than 10 micro molar.

Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid used in the present method may inhibit enzyme activity through a variety of mechanisms. By the way of example, and without limitation, the inhibitors used in the methods described herein may block the enzyme activity directly by acting as a substrate for the enzyme.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH2-) radical.

Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl.

The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

The terms "alkenyl", "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

The term "heterocyclyl" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

The term "heteroaryl" embraces unsaturated heterocyclyl radicals. Examples of unsaturated heterocyclyl radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.;

unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclyl radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals -SO2-. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide

haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote NH2O2S-.

The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl.

The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes -(C=O)-.

The term "aroyl" embraces aryl radicals with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -CO2H.

The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl.

The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl porions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

The term "heterocyclylalkyl" embraces saturated and partially unsaturated heterocyclyl-substituted alkyl radicals, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals.

The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an oxygen atom to an alkyl radical.

The term "aralkylthio" embraces aralkyl radicals attached to a sulfur atom.

The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical.

The term "aminoalkyl" embraces alkyl radicals substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like.

The term "alkylamino" denotes amino groups that have been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

The term "aralkylamino" embraces aralkyl radicals attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

The term "aminocarbonyl" denotes an amide group of the formula -C(=O)NH2.

The term "alkylaminocarbonyl" denotes an aminocarbonyl group which has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower

N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above.

The term "alkylaminoalkyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical.

The term "aryloxyalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent oxygen atom.

The term "arylthioalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

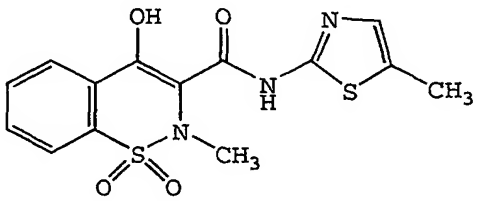
Description of the Preferred Embodiments

It has been discovered that inhibition or prevention of cardiovascular disease, and in particular vascular restenosis, is provided by a combination therapy comprising administering to a subject a cyclooxygenase-2 selective inhibitor along with a dose of radiation. Restenosis, as detailed above, occurs due to the interaction of numerous biological events, including a wound healing response and an inflammatory response, that are triggered as a result of procedures such as coronary angioplasty. It is known in the art that ionizing radiation ameliorates the wound healing response. Further, it is also known in the art that cyclooxygenase-2 selective inhibitors are potent anti-inflammatory agents. The presently described combination therapy is beneficial for the treatment of cardiovascular disease, therefore, without being bound to any particular theory, because cyclooxygenase-2 selective inhibitors and radiation each attenuate independent biological events that are known to cause restenosis. Thus, the coupling of a cyclooxygenase-2 selective inhibitor and radiation provides a synergistic therapy for the treatment of cardiovascular disease. Moreover, the use of cyclooxygenase-2 selective inhibitors is highly advantageous in that it minimizes the gastric side effects that can occur with non-selective NSAID's, especially where prolonged treatment is expected.

The present method, accordingly, can be used for the prevention or inhibition of restenosis following vascular intervention such as angioplasty, grafting, stent placement, endarterectomy, atherectomy (including rotational, directional and extraction atherectomy), or excimer laser therapy of coronary stenosis. In one embodiment, the method can be used for preventing or inhibiting restenosis following angioplasty and in

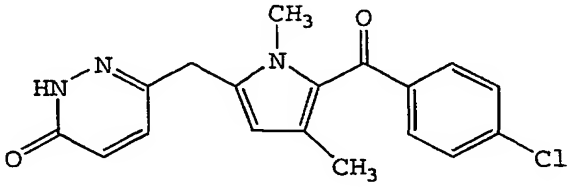
particular coronary artery angioplasty (percutaneous transluminal coronary angioplasty or PTCA). In another embodiment, the method can be used for preventing or inhibiting restenosis following vascular grafting and in particular, coronary artery bypass grafting (CABG).

Any cyclooxygenase-2 selective inhibitor or prodrug or pharmaceutically acceptable salt thereof may be employed in the method of the present invention. In one embodiment, the cyclooxygenase-2 selective inhibitor can be, for example, the cyclooxygenase-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7) or a pharmaceutically acceptable salt or prodrug thereof.



B-1

In yet another embodiment, the cyclooxygenase-2 selective inhibitor is the cyclooxygenase-2 selective inhibitor, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3) or a pharmaceutically acceptable salt or prodrug thereof.

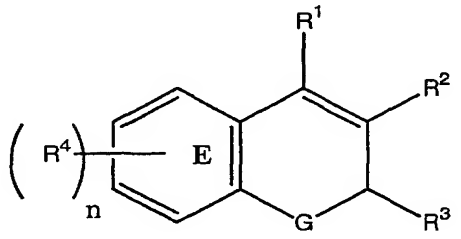


B-2

In a preferred embodiment the cyclooxygenase-2 selective inhibitor is preferably of the chromene structural class that is a substituted benzopyran or a substituted benzopyran analog, and even more preferably selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the general Formula I shown below and possessing, by way of example and not limitation, the structures disclosed in Table 1, including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof. Furthermore, benzopyran cyclooxygenase-2 selective inhibitors useful in the practice of the present methods are

described in U.S. Patent No. 6,034,256 and 6,077,850 herein incorporated by reference in their entirety.

In one embodiment, the cyclooxygenase-2 selective inhibitor is of the chromene structural class and is represented by Formula I:



(I)

or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof;

wherein n is an integer which is 0, 1, 2, 3 or 4;

wherein G is O, S or NR^a;

wherein R^a is alkyl;

wherein R^1 is selected from the group consisting of H and aryl;

wherein R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

wherein R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or NR^b;

R^1 is H;

R^b is alkyl;

R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

each R^4 is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

In a further embodiment, the cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I), or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof; wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is oxygen or sulfur;

R^1 is H;

R^2 is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

R^3 is lower haloalkyl, lower cycloalkyl or phenyl; and

each R^4 is H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or

wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof; wherein:

R^2 is carboxyl;

R^3 is lower haloalkyl; and

each R^4 is H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof; wherein:

n is an integer which is 0, 1, 2, 3 or 4;

R^3 is fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, or trifluoromethyl; and

each R^4 is H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof; wherein:

n is an integer which is 0, 1, 2, 3 or 4;

R^3 is trifluoromethyl or pentafluoroethyl; and

each R^4 is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

In yet another embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound having the structure of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:

wherein:

n = 4;

G is O or S;

R^1 is H;

R^2 is CO_2H;

R^3 is lower haloalkyl;

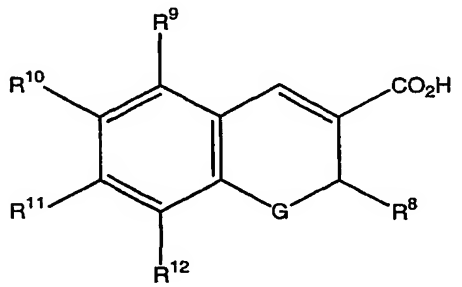
a first R^4 corresponding to R^9 is hydrido or halo;

a second R^4 corresponding to R^{10} is H, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, or 6- membered nitrogen-containing heterocyclosulfonyl;

a third R^4 corresponding to R^{11} is H, lower alkyl, halo, lower alkoxy, or aryl; and

a fourth R^4 corresponding to R^{12} is H, halo, lower alkyl, lower alkoxy, and aryl;

wherein Formula (I) is represented by Formula (Ia):



(Ia)

or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

The cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound of having the structure of Formula (Ia) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof; wherein:

R^8 is trifluoromethyl or pentafluoroethyl;

R^9 is H, chloro, or fluoro;

R^{10} is H, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, or morpholinosulfonyl;

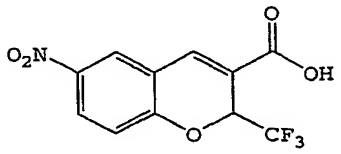
R^{11} is H, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, or phenyl; and

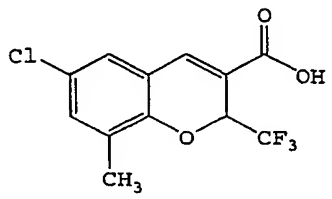
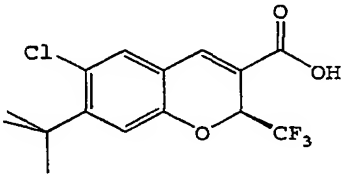
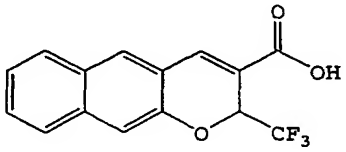
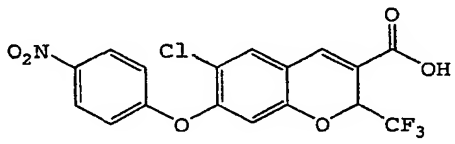
R^{12} is H, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, or phenyl.

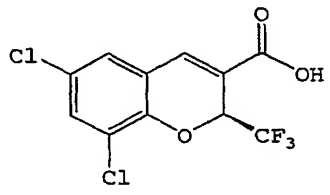
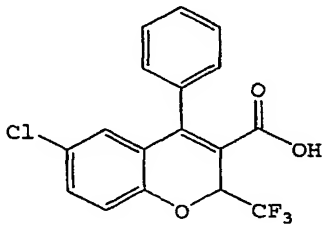
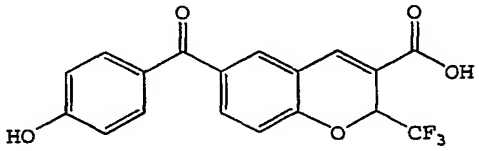
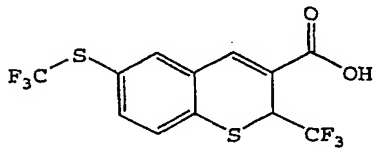
Examples of exemplary chromene cyclooxygenase-2 selective inhibitors are depicted in Table 1 below.

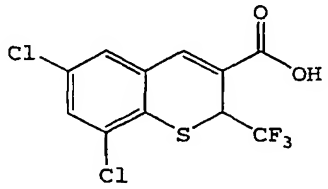
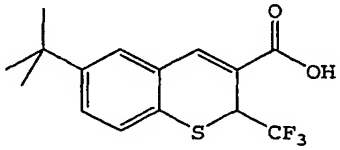
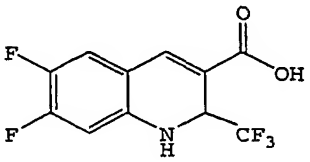
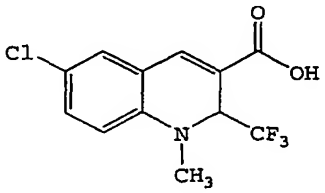
Table 1

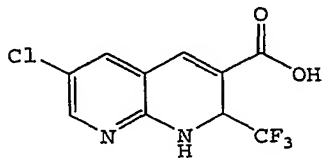
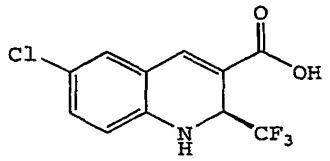
Examples of Chromene Cyclooxygenase-2 Selective Inhibitors as Embodiments

Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid

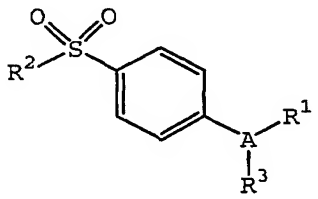
Compound Number	Structural Formula
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1- benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

In a further preferred embodiment, the cyclooxygenase inhibitor is selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of Formula II:



II

wherein A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R^1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino,

alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

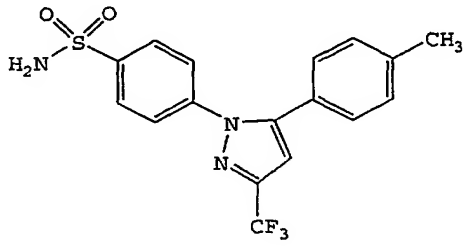
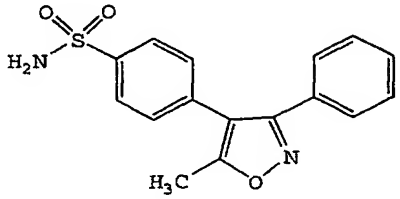
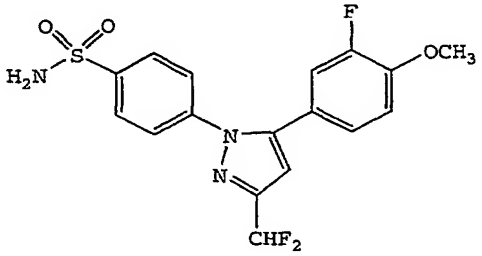
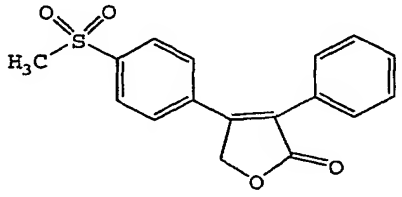
wherein R^2 is selected from the group consisting of methyl or amino; and

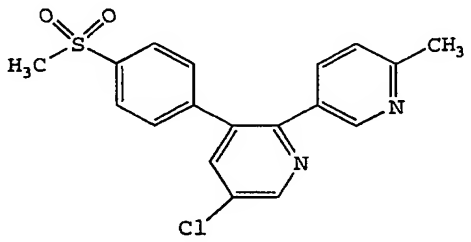
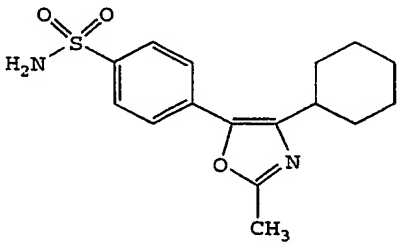
wherein R^3 is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl; or a pharmaceutically acceptable salt thereof.

In a still more preferred embodiment of the invention the cyclooxygenase-2 selective inhibitor represented by the above Formula II is selected from the group of compounds, illustrated in Table 2, consisting of celecoxib (B-18; U.S. Patent No. 5,466,823; CAS No. 169590-42-5), valdecoxib (B-19; U.S. Patent No. 5,633,272; CAS No. 181695-72-7), deracoxib (B-20; U.S. Patent No. 5,521,207; CAS No. 169590-41-4), rofecoxib (B-21; CAS No. 162011-90-7), etoricoxib (MK-663; B-22; PCT publication WO 98/03484), JTE-522 (B-23), or an isomer, ester, a pharmaceutically acceptable salt or prodrug thereof.

Table 2.

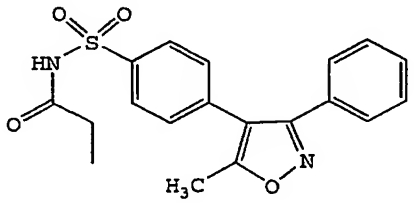
Examples of Tricyclic Cyclooxygenase-2 Selective Inhibitors as Embodiments

Compound Number	Structural Formula
B-18	
B-19	
B-20	
B-21	

Compound Number	Structural Formula
B-22	
B-23	

In an even more preferred embodiment, the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

In another highly preferred embodiment of the invention, parecoxib (B-24, U.S. Patent No. 5,932,598, CAS No. 198470-84-7), which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, may be advantageously employed as a source of a cyclooxygenase inhibitor (US 5,932,598, herein incorporated by reference).

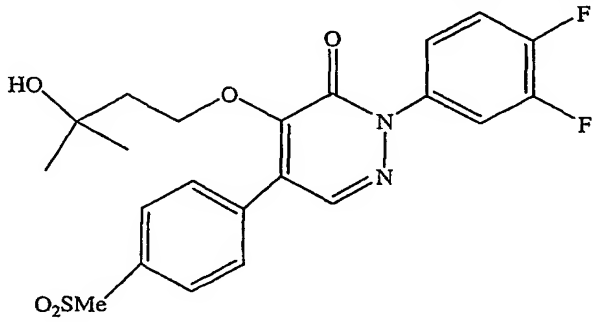


B-24

A preferred form of parecoxib is sodium parecoxib.

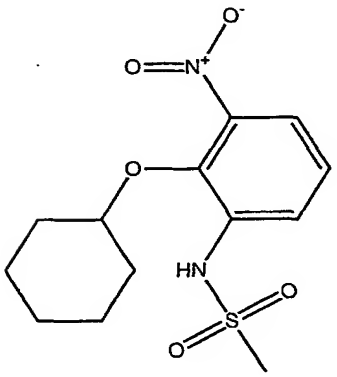
In another preferred embodiment of the invention, the compound having the formula B-25 that has been previously described in International Publication number

WO 00/24719 (which is herein incorporated by reference), is another tricyclic cyclooxygenase-2 selective inhibitor which may be advantageously employed.



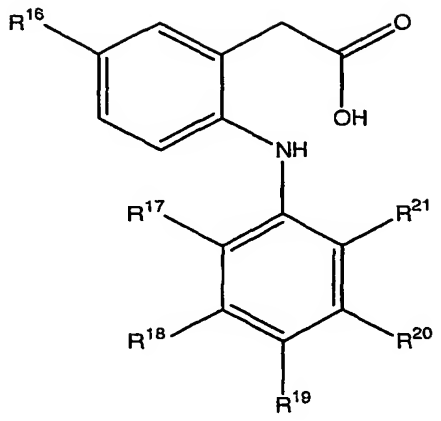
B-25

Another preferred cyclooxygenase-2 selective inhibitor that is useful in connection with the method(s) of the present invention is N-(2-cyclohexyloxynitrophenyl)-methane sulfonamide (NS-398) having a structure shown below as B-26.



B-26

In yet a further preferred embodiment of the invention, the cyclooxygenase inhibitor used in connection with the method(s) of the present invention can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula (III):



(III)

or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof;

wherein

R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl,

provided that R^{17}, R^{18}, R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H.

A particularly preferred phenylacetic acid derivative cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention is a compound that has the designation of COX 189 (B-211) and that has the structure shown in Formula (III) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

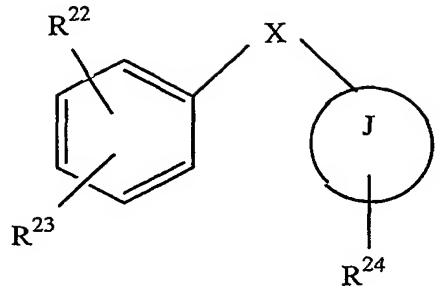
R^{16} is ethyl;

R^{17} and R^{19} are chloro;

R^{18} and R^{20} are hydrogen; and

and R^{21} is methyl.

In yet another embodiment, the cyclooxygenase-2 selective inhibitor is represented by Formula (IV):



(IV)

or an isomer, a pharmaceutically acceptable salt, an ester, or a prodrug thereof,

wherein:

X is O or S;

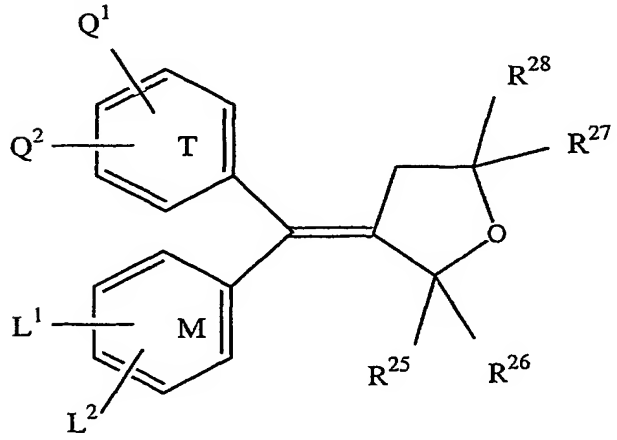
J is a carbocycle or a heterocycle;

R^{22} is $NHSO_2CH_3$ or F;

R^{23} is H, NO_2, or F; and

R^{24} is H, $NHSO_2CH_3$, or $(SO_2CH_3)C_6H_4$.

According to another embodiment, the cyclooxygenase-2 selective inhibitors used in the present method(s) have the structural Formula (V):



(V)

or an isomer, a pharmaceutically acceptable salt, an ester, or a prodrug thereof, wherein:

T and M independently are phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

Q^1, Q^2, L^1 or L^2 are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, or lower methoxy having from 1 to 6 carbon atoms; and

at least one of Q^1, Q^2, L^1 or L^2 is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or,

Q^1 and Q^2 are methylenedioxy; or

L^1 and L^2 are methylenedioxy; and

R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{25} and R^{26} are O; or,

R^{27} and R^{28} are O; or,

R^{25}, R^{26}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or,

R^{27}, R^{28}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms.

In a particularly preferred embodiment, the compounds N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl] benzenesulfonamide having the structure of Formula (V) are employed as cyclooxygenase-2 selective inhibitors.

Exemplary compounds that are useful for the cyclooxygenase-2 selective inhibitor in connection with the method(s) of the present invention, the structures for which are set forth in Table 3 below, include, but are not limited to:

6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-27);

6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-28);

8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-29);

6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-30);

2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid (B-31);

7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-32);

6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-33);
8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-34);
6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-35);
5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-36);
8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-37);
7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-38);
6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-39);
7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-40);
7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-41);
6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-42);
6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-43);
6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-44);
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-45);
6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-46);
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-47);
8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-48)
8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-49);
6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-50);
8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-51);
8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-52);
8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-53);
6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-54);
6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-55);
6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-56);
6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-57);
6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-58);
6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-59);
6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-60);

6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-61);
6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-62);
8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-63);
6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-64);
6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-65);
8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-66);
6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-67);
6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-68);
6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-69);
6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-70);
6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-71);
7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid (B-72);
6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-73);
3-[(3-Chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070 (B-74);
8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine (B-75);
5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone (B-76);
5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (B-77);
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole (B-78);
4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-79);
4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-80);
4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-81);
4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-82);
4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-83);
4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-84);
4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-85);

4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-86);
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-87);
4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-88);
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-89);
4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-90);
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-91);
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-92);
4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-93);
4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-94);
4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-95);
4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-96);
4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-97);
4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-98);
4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-99);
4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-100);
4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-101);
4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-102);
5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-103);
4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-104);
6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene (B-105);
5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-106);
4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-107);
5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-108);
5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-109);
4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-110);

2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (B-111);

2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (B-112);

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole (B-113);

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-114);

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole (B-115);

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole (B-116);

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole (B-117);

2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole (B-118);

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-119);

1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene (B-120);

4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide (B-121);

5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene (B-122);

4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide (B-123);

6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-124);

2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-125);

6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile (B-126);

4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-127);

4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-128);

4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-129);

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-130);

2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-131);

2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-132);

2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-133);

4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-134);

2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-135);

4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-136);

2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole (B-137);

2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole (B-138);

2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (B-139);

2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole (B-140);

1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole (B-141);

2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-142);

4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-143);

2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-144);

4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-145);

2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-146);

4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-147);

1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole (B-148);

4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-149);

4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-150);

4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-151);

1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-152);

4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide (B-153);

N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide (B-154);

ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate (B-155);

4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole (B-156);

4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole (B-157);

1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-158);

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole (B-159);

4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole (B-160);

5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-161);

2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-162);

5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine (B-163);

2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-164);

4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (B-165);

1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (B-166);

5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole (B-167);

4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide (B-168);

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-169);

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-170);

4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide (B-171);

1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-172);

1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-173);
1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-174);
1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-175);
1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-176);
1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-177);
1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-178);
4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide (B-179);
1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-180);
4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide (B-181);
4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-182);
4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-183);
1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-184);
1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-185);
4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide (B-186);
1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-187);
4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-188);
4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide (B-189);
ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate (B-190);
2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid (B-191);
2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole (B-192);
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (B-193);
4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole (B-194);
4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (B-195);
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-196);
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-197);
5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone (B-198);
6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-199);
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-200);

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-201);

4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-202);

3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-203);

2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-204);

4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-205);

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-206);

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-207);

[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide (B-208);

4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide (B-209);

4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (B-210);

[2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid or COX 189 (B-211);

N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide (B-212);

N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide or flosulide (B-213);

N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, soldium salt or L-745337 (B-214);

N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide or RWJ-63556 (B-215);

3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one or L-784512 or L-784512 (B-216);

(5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4(5H)-thiazolone or darbufelone (B-217);

CS-502 (B-218);

LAS-34475 (B-219);

LAS-34555 (B-220);

S-33516 (B-221);

SD-8381 (B-222);

L-783003 (B-223);

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide or T-614 (B-224);

D-1367 (B-225);

L-748731 (B-226);

(6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid or CT3 (B-227);

CGP-28238 (B-228);

4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389 (B-229);

GR-253035 (B-230);

6-dioxo-9H-purin-8-yl-cinnamic acid (B-231);

S-2474 (B-232);

4-[4-(methyl)-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

4-(5-methyl-3-phenyl-4-isoxazolyl);

2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl];

N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl];

4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;

2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridzainone;

2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

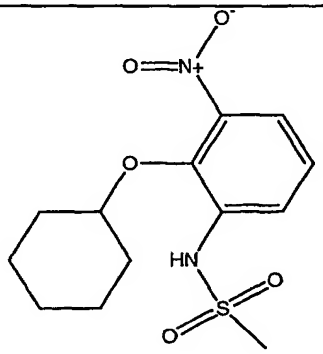
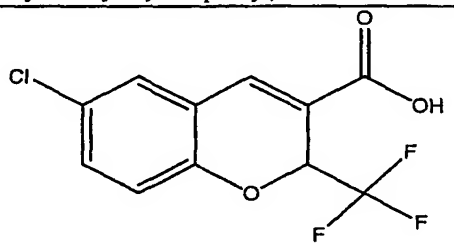
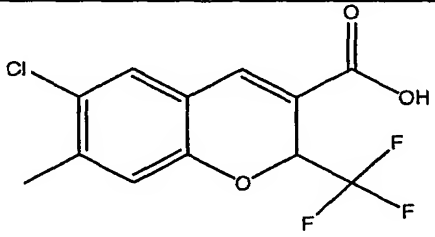
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

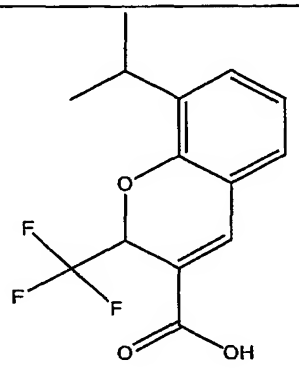
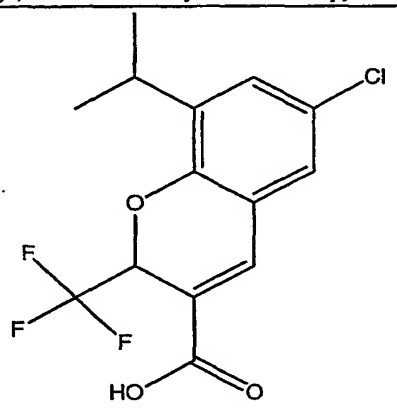
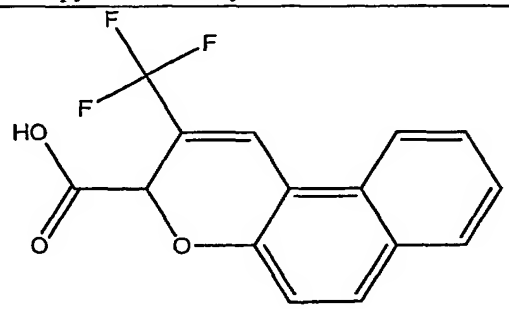
[2-(2,4-dichloro-6-ethyl-3,5-dimethyl-phenylamino)-5-propyl-phenyl]-acetic acid;

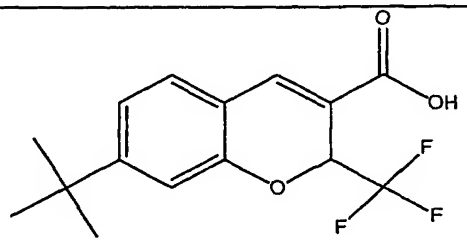
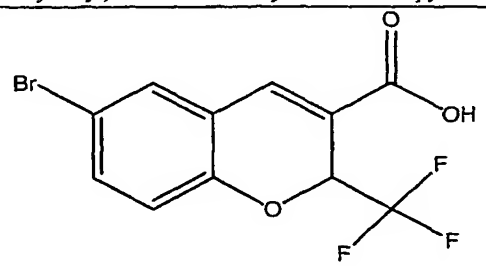
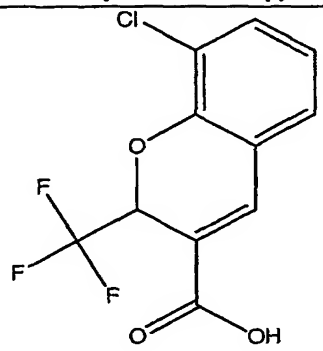
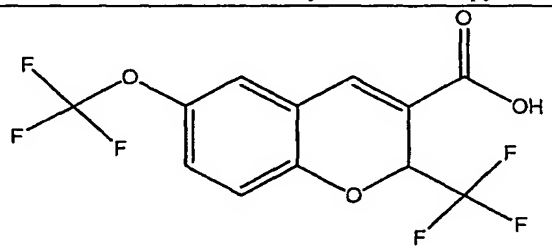
or an isomer, a pharmaceutically acceptable salt, ester or prodrug thereof..

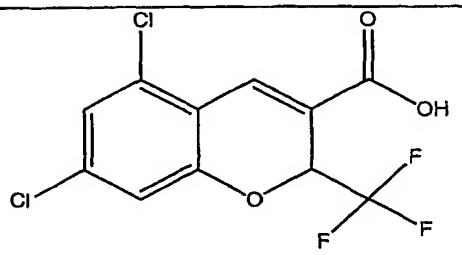
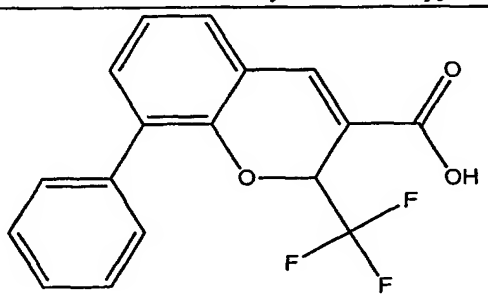
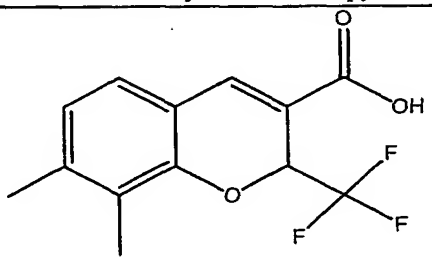
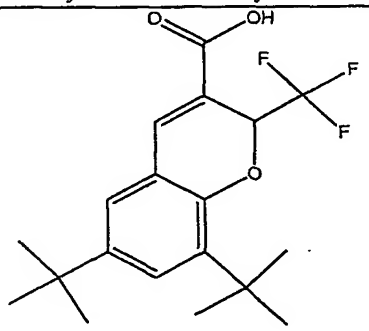
Table 3

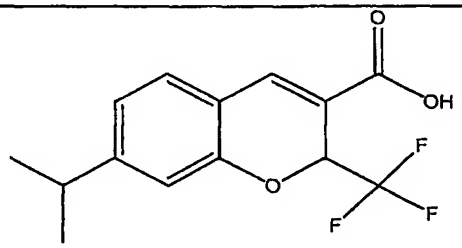
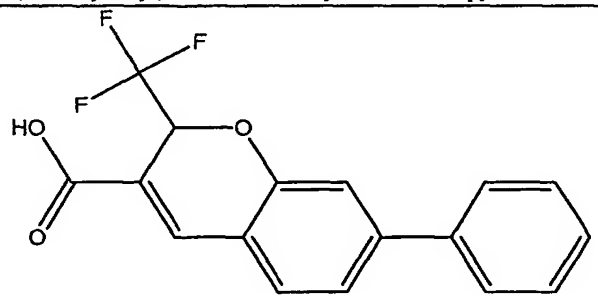
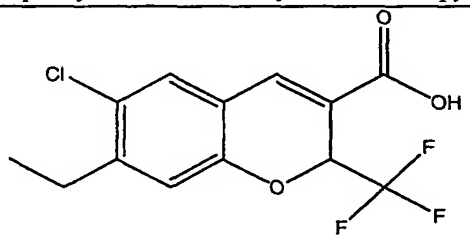
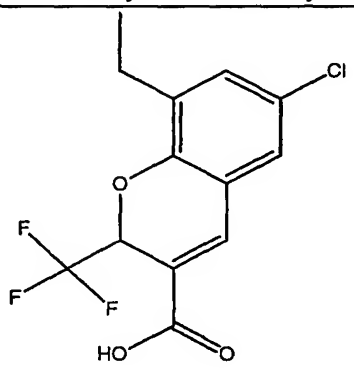
Examples of Cyclooxygenase-2 Selective Inhibitors as Embodiments

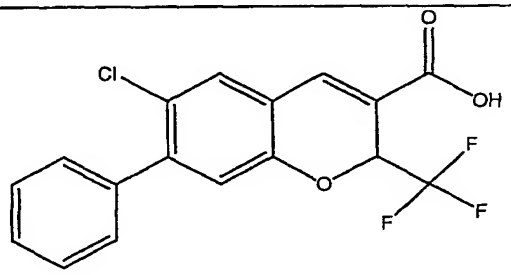
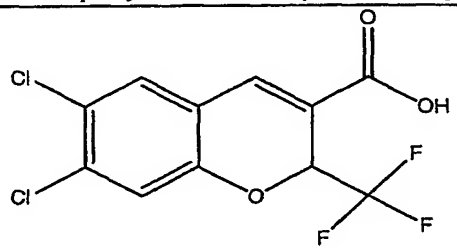
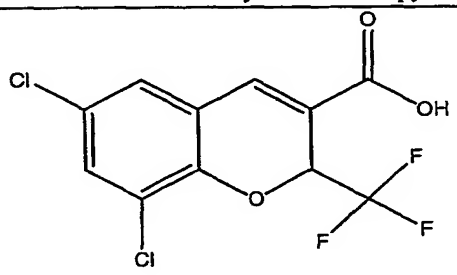
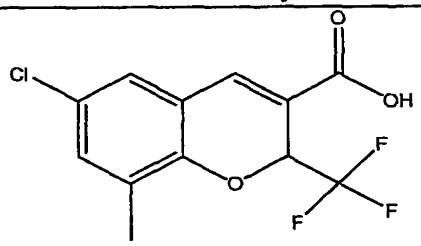
Compound Number	Structural Formula
B-26	 N-(2-cyclohexyloxynitrophenyl) methane sulfonamide or NS-398;
B-27	 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-28	 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

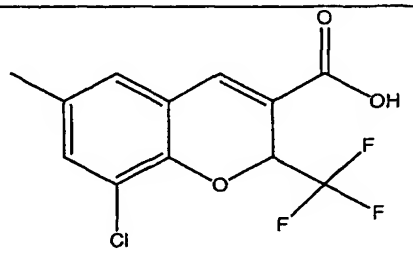
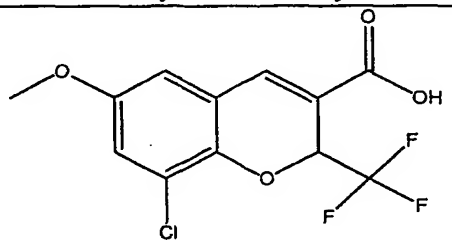
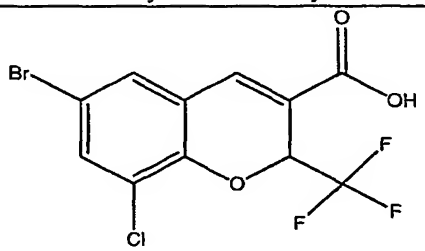
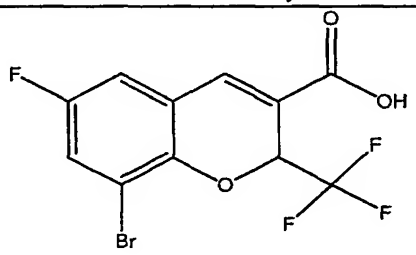
Compound Number	Structural Formula
B-29	 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-30	 6-chloro-8-(1-methylethyl)-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-31	 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;

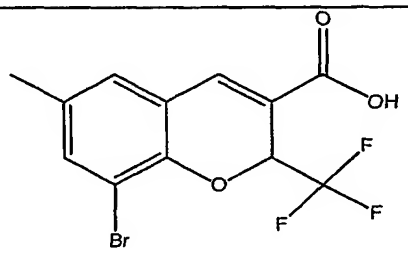
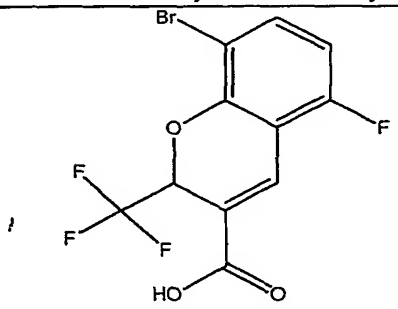
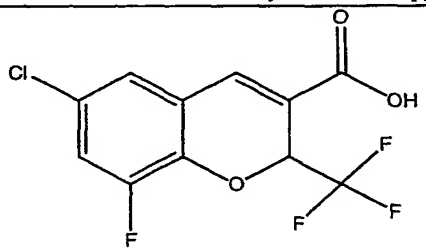
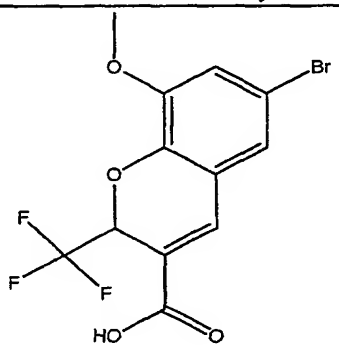
Compound Number	Structural Formula
B-32	 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-33	 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-34	 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-35	 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

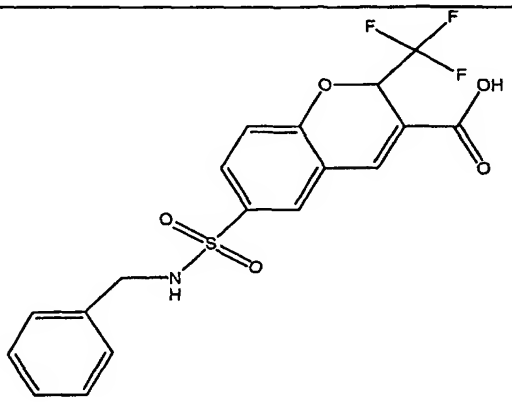
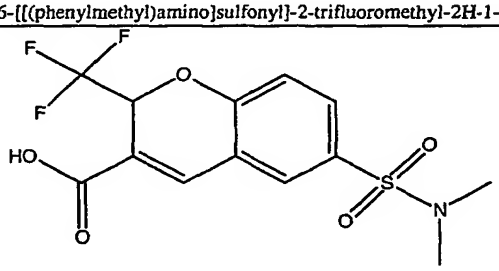
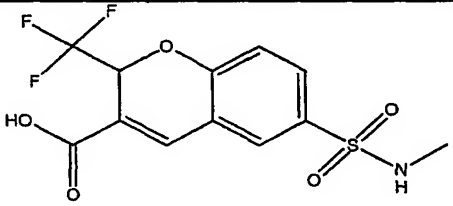
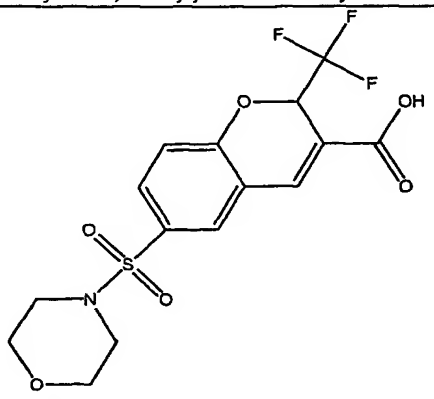
Compound Number	Structural Formula
B-36	 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-37	 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-38	 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-39	 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

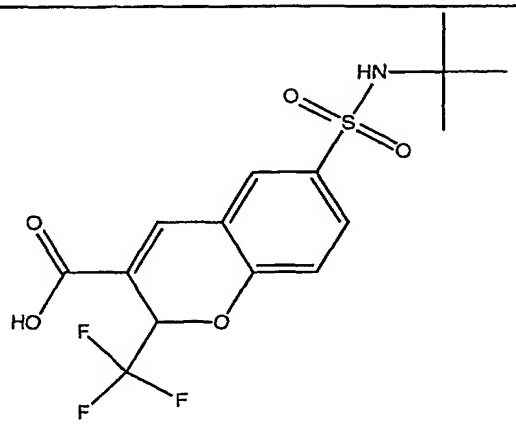
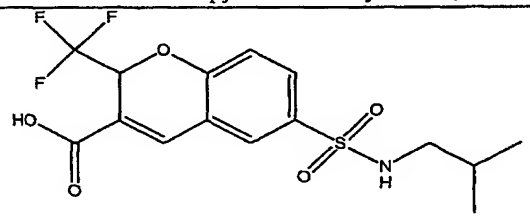
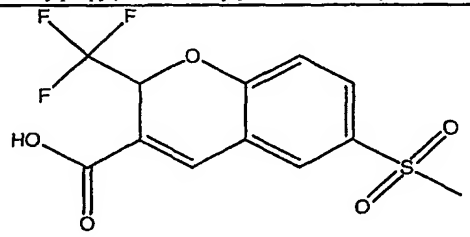
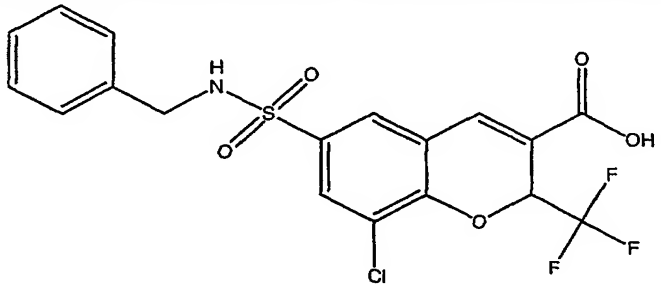
Compound Number	Structural Formula
B-40	 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-41	 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-42	 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-43	 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

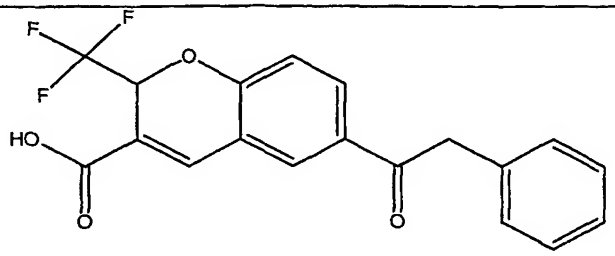
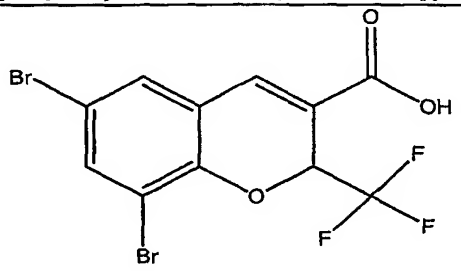
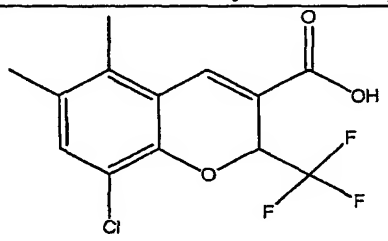
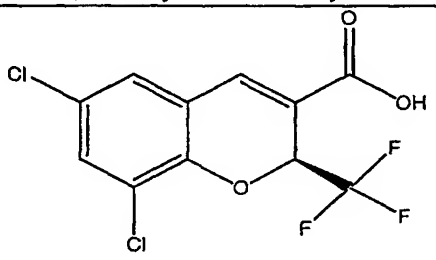
Compound Number	Structural Formula
B-44	 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-45	 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-46	 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-47	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

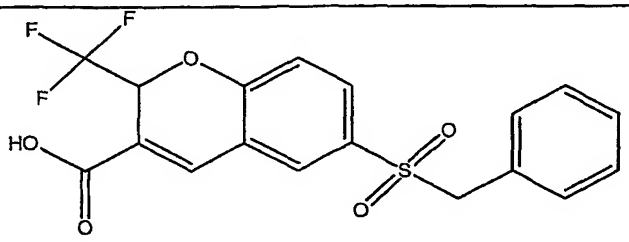
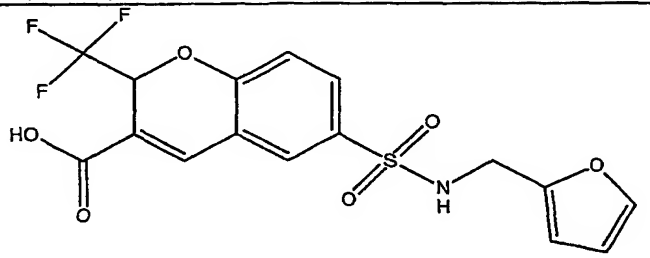
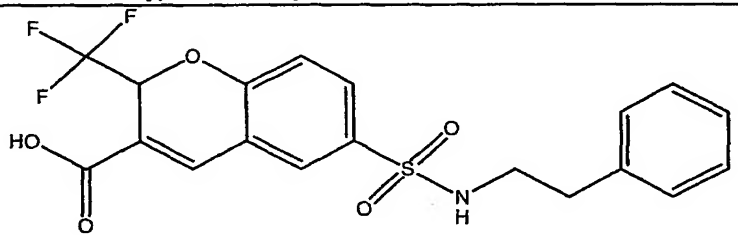
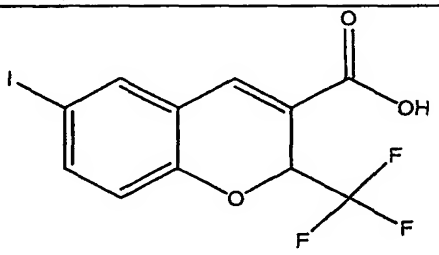
Compound Number	Structural Formula
B-48	 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-49	 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-50	 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-51	 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

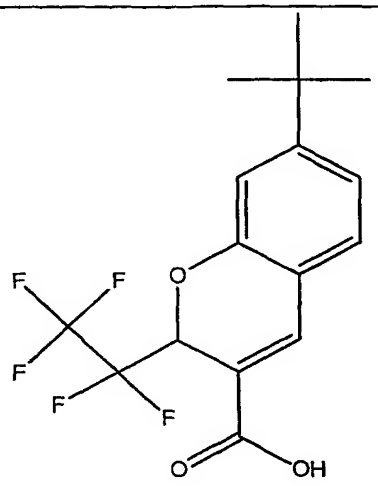
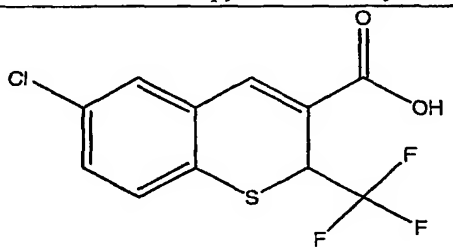
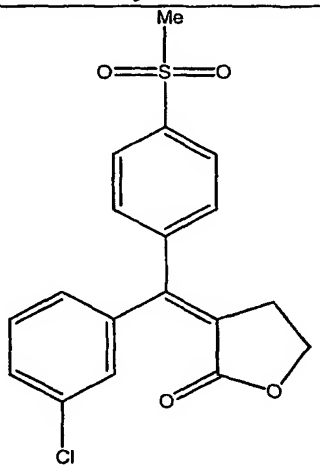
Compound Number	Structural Formula
B-52	 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-53	 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-54	 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-55	 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

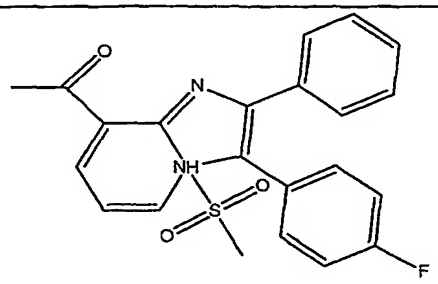
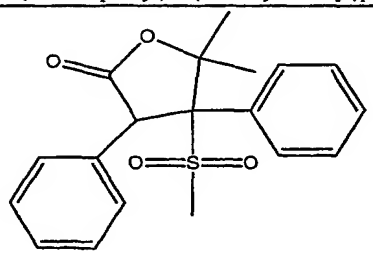
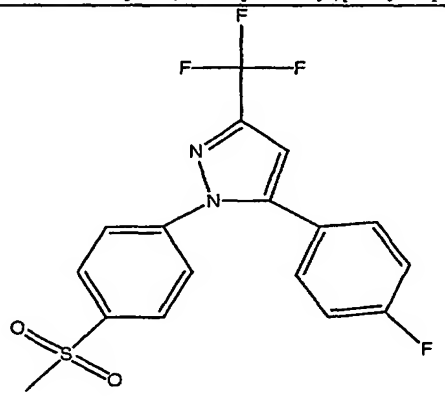
Compound Number	Structural Formula
B-56	 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-57	 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-58	 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-59	 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

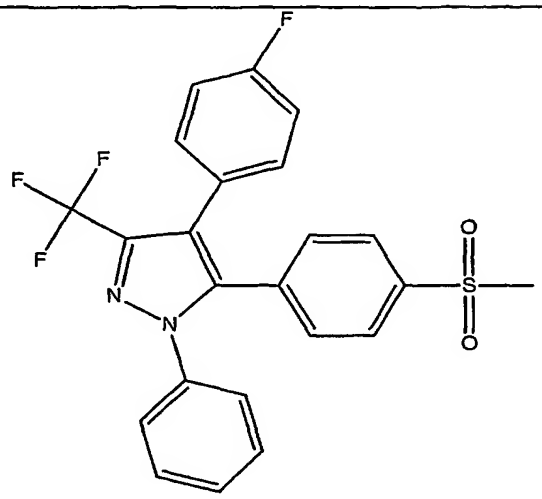
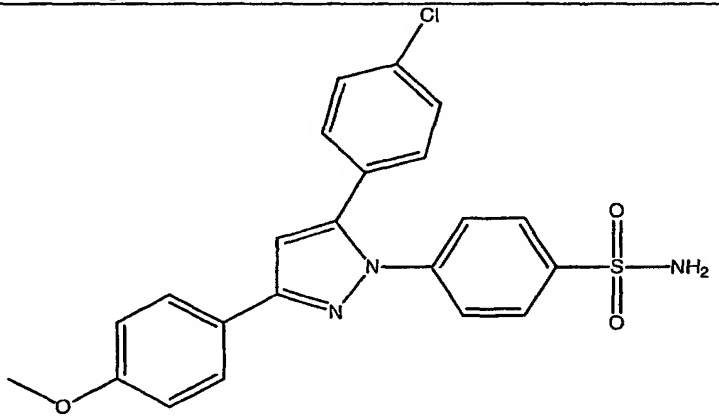
Compound Number	Structural Formula
B-60	 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-61	 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-62	 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-63	 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl- 2H-1-benzopyran-3-carboxylic acid;

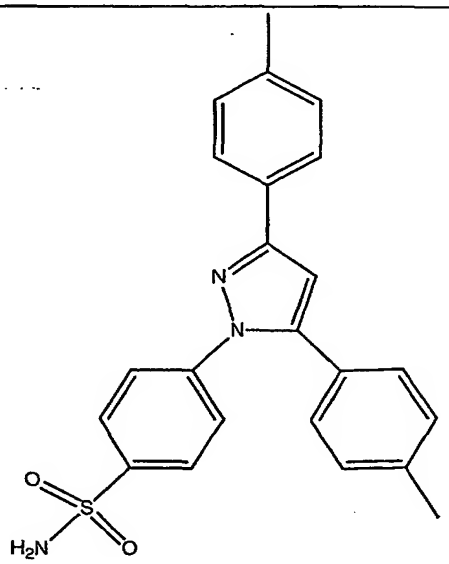
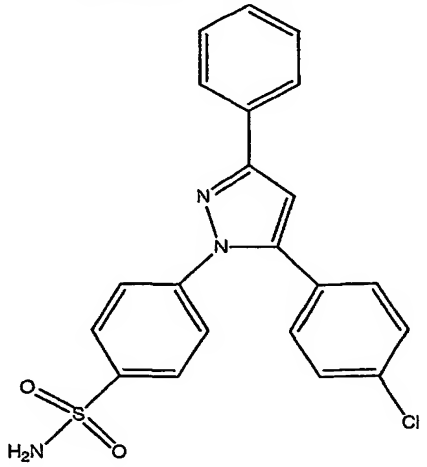
Compound Number	Structural Formula
B-64	 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-65	 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-66	 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-67	 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

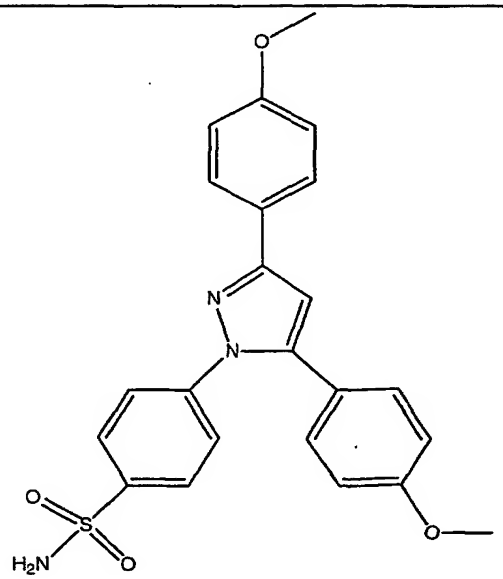
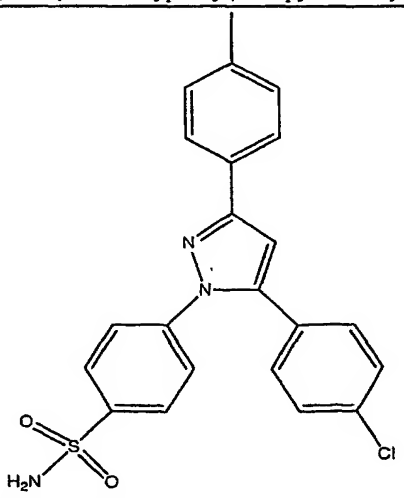
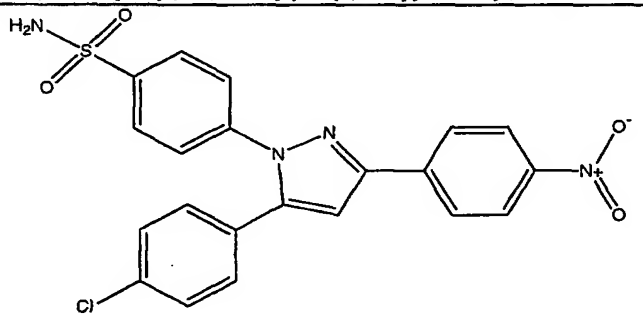
Compound Number	Structural Formula
B-68	 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-69	 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-70	 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran -3-carboxylic acid;
B-71	 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

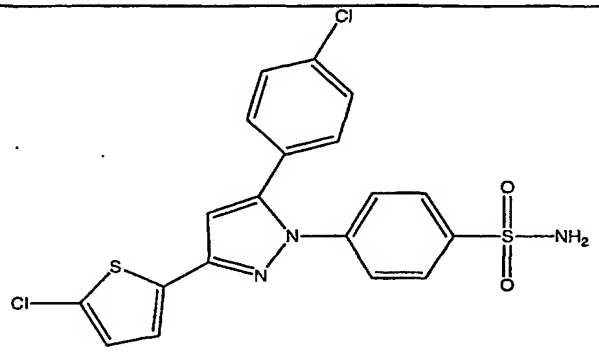
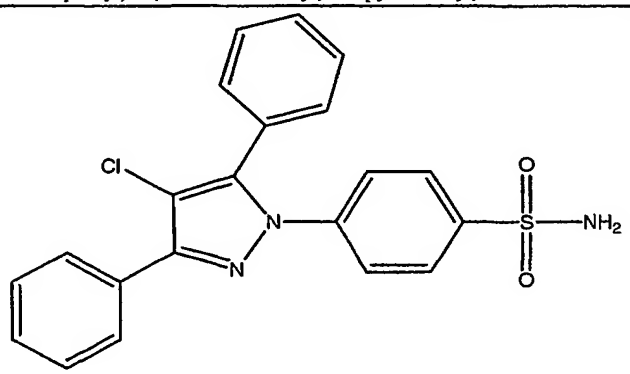
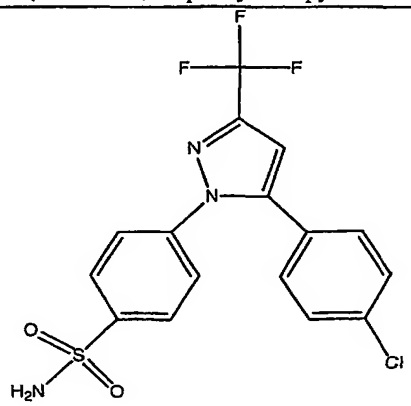
Compound Number	Structural Formula
B-72	 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H -1-benzopyran-3-carboxylic acid;
B-73	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
B-74	 3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene] -dihydro-furan-2-one or BMS-347070;

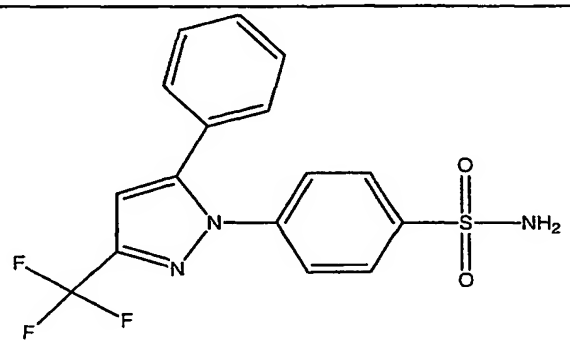
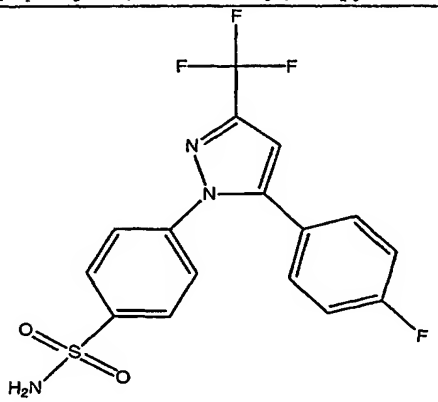
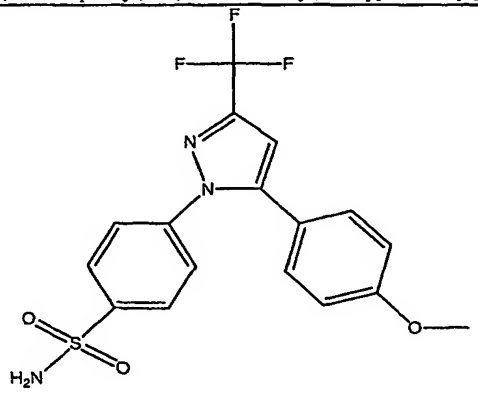
Compound Number	Structural Formula
B-75	 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;
B-76	 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;
B-77	 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

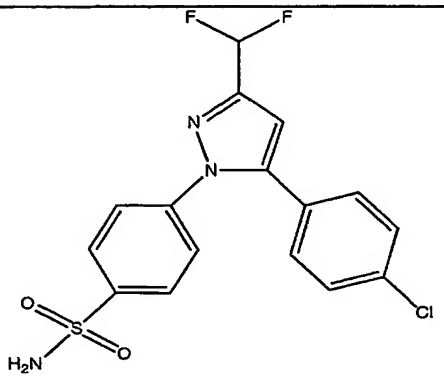
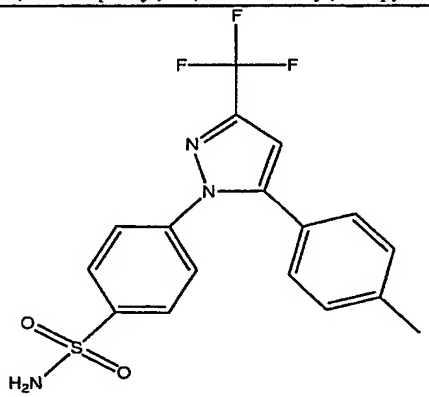
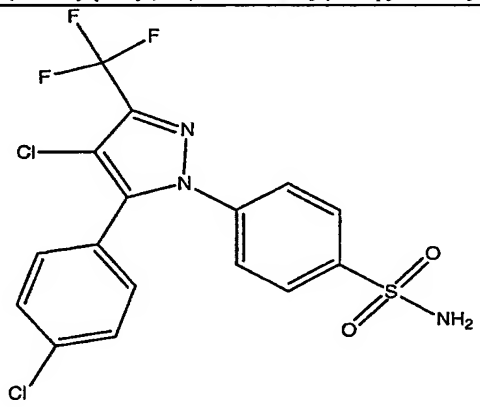
Compound Number	Structural Formula
B-78	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -1-phenyl-3-(trifluoromethyl)pyrazole;
B-79	 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide;

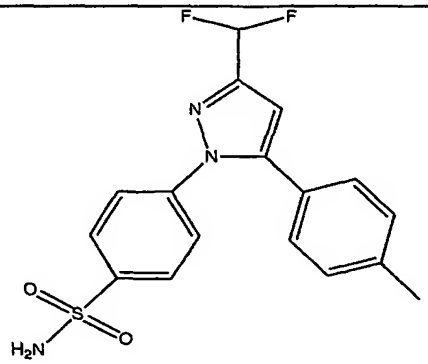
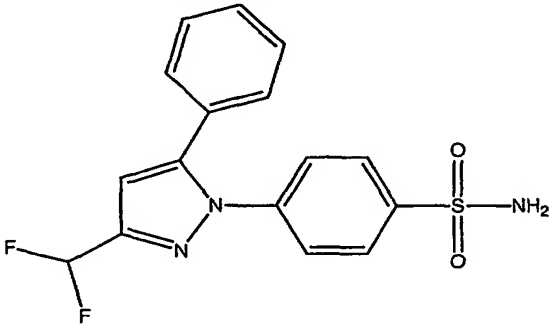
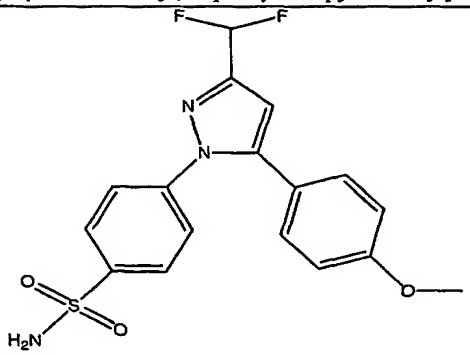
Compound Number	Structural Formula
B-80	 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-81	 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

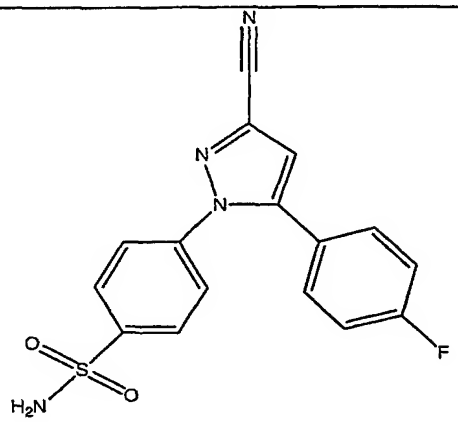
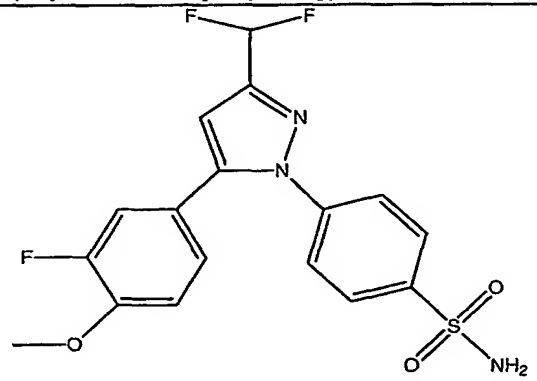
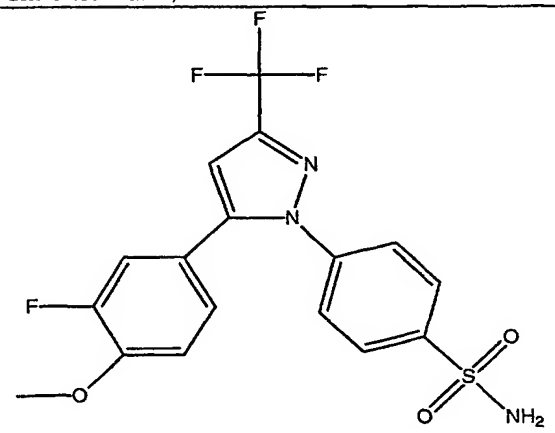
Compound Number	Structural Formula
B-82	 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-83	 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-84	 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

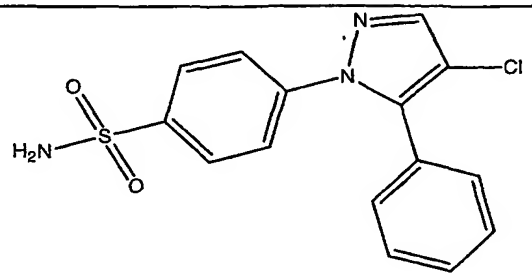
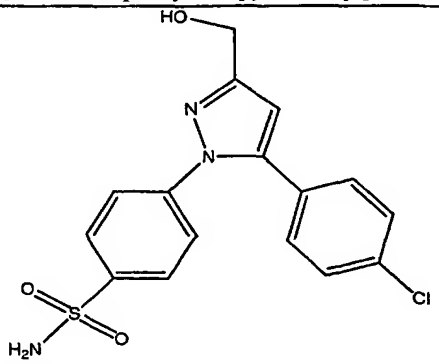
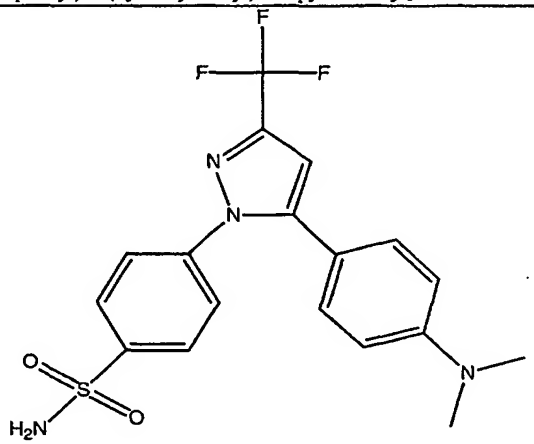
Compound Number	Structural Formula
B-85	 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-86	 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;
B-87	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

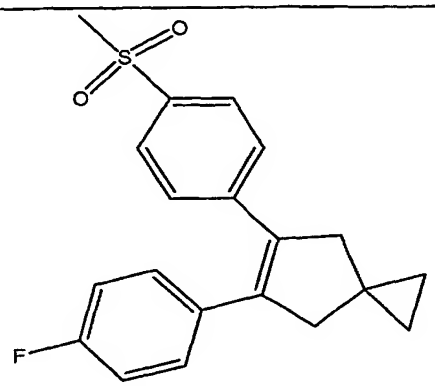
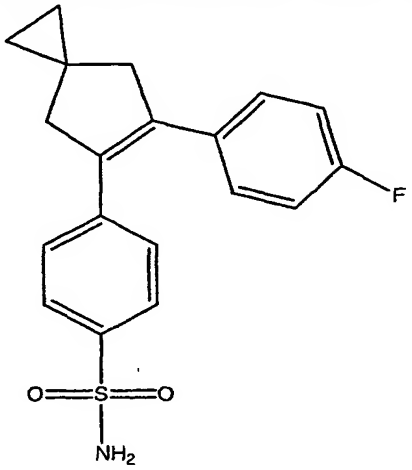
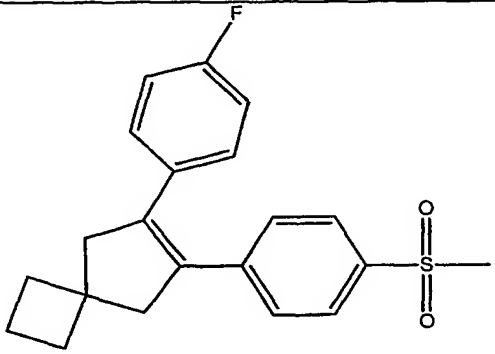
Compound Number	Structural Formula
B-88	 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-89	 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-90	 4[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

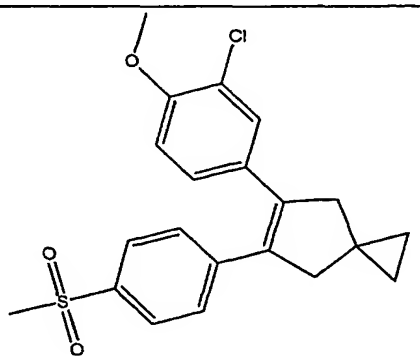
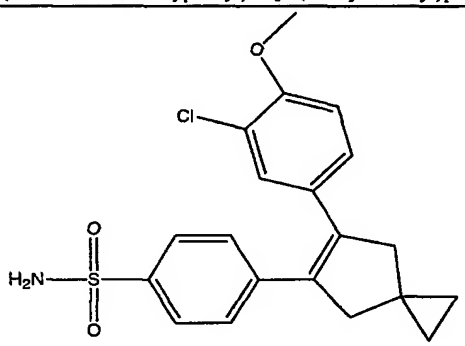
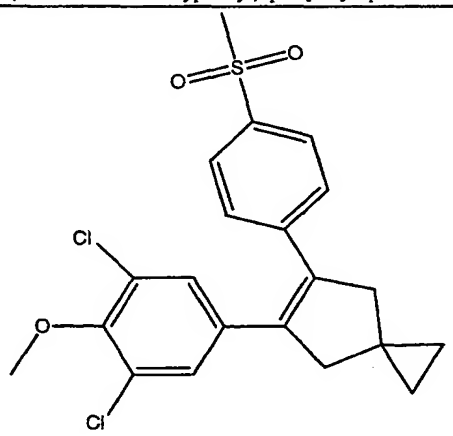
Compound Number	Structural Formula
B-91	 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-92	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-93	 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

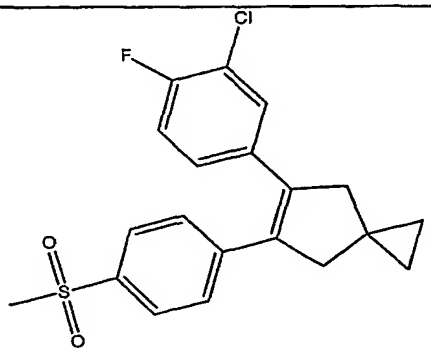
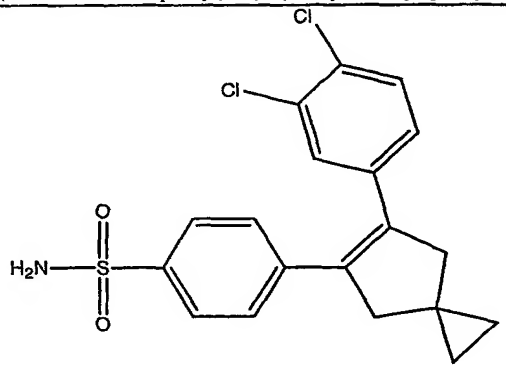
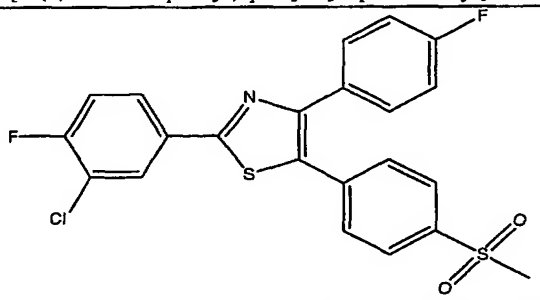
Compound Number	Structural Formula
B-94	 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-95	 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-96	 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

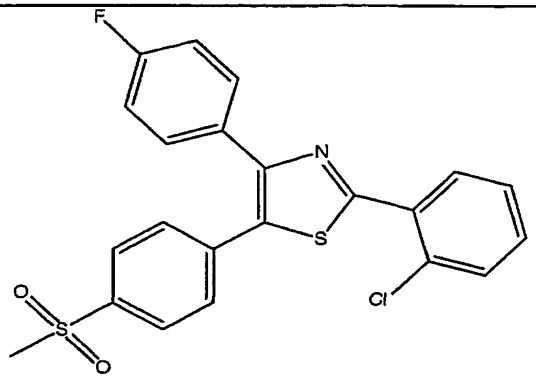
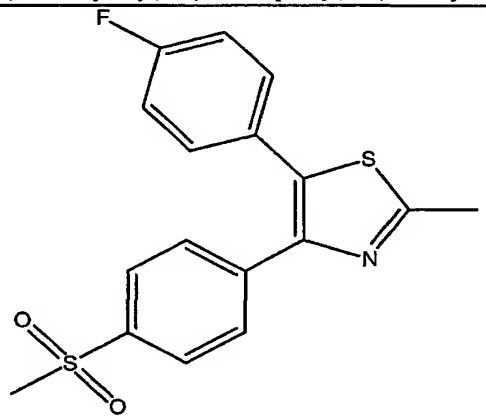
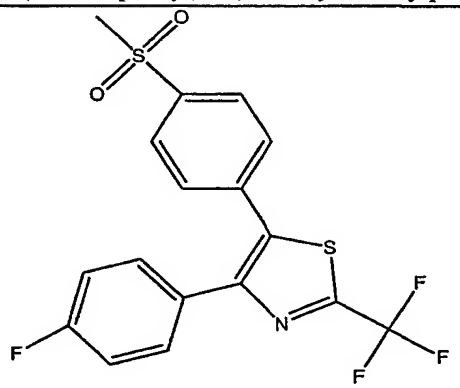
Compound Number	Structural Formula
B-97	 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-98	 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide;
B-99	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

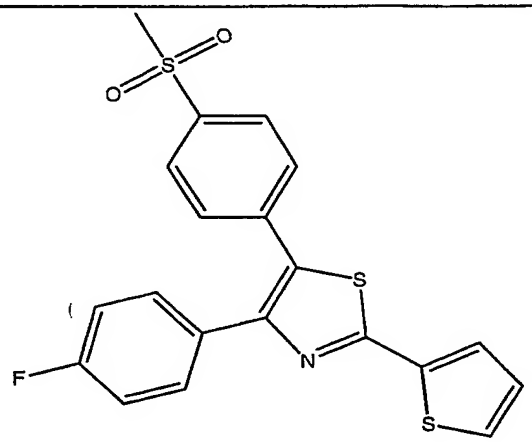
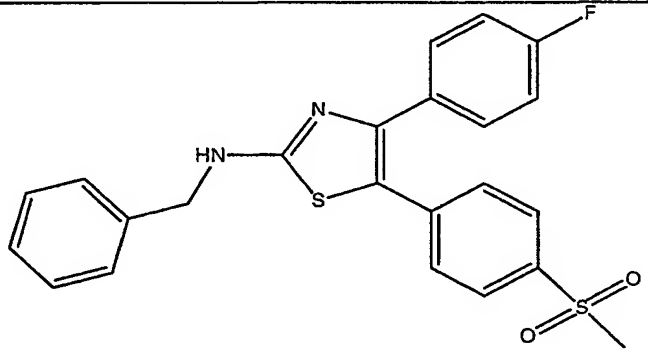
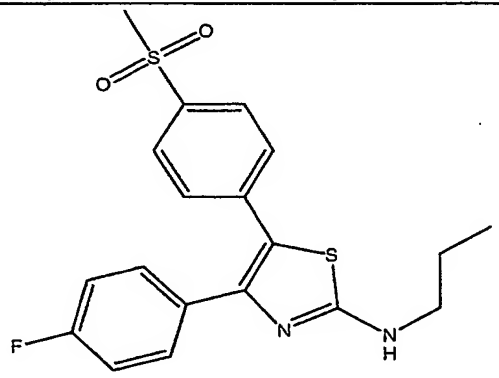
Compound Number	Structural Formula
B-100	 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-101	 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-102	 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;

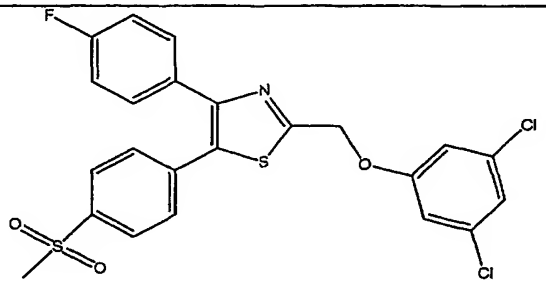
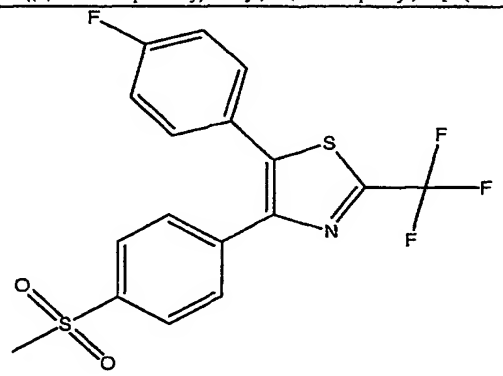
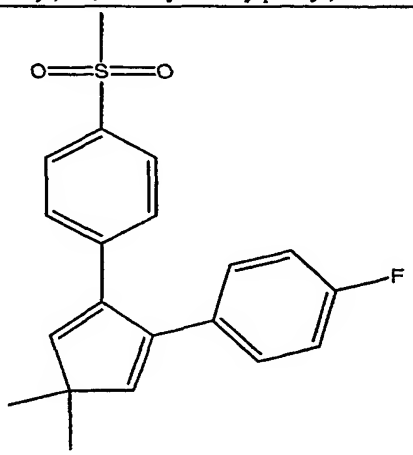
Compound Number	Structural Formula
B-103	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-104	 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-105	 6-(4-fluorophenyl)-7-[4-methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

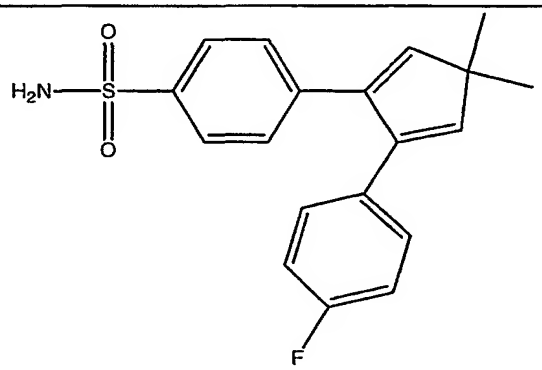
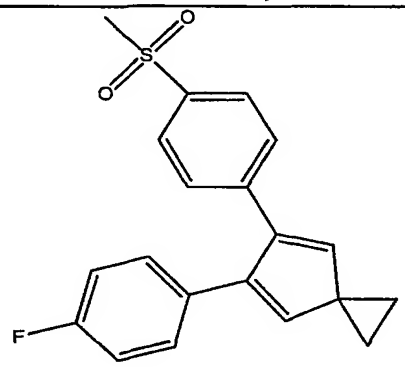
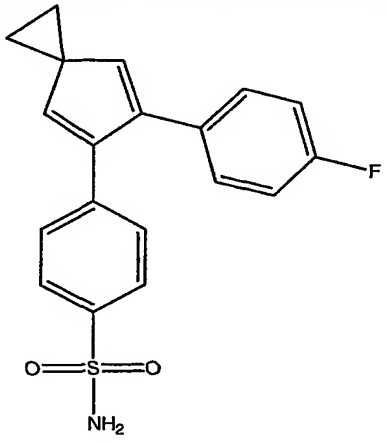
Compound Number	Structural Formula
B-106	 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-107	 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-108	 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene;

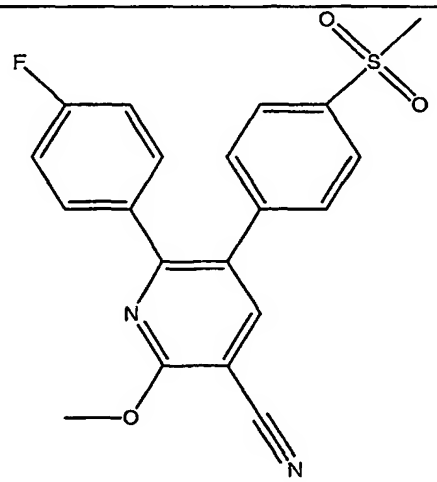
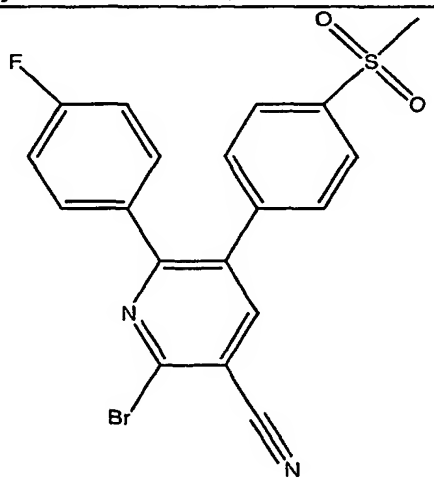
Compound Number	Structural Formula
B-109	 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-110	 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-111	 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

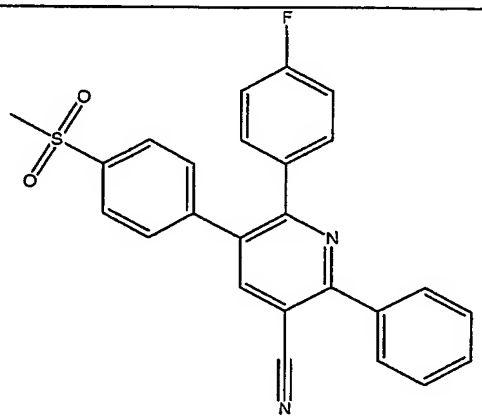
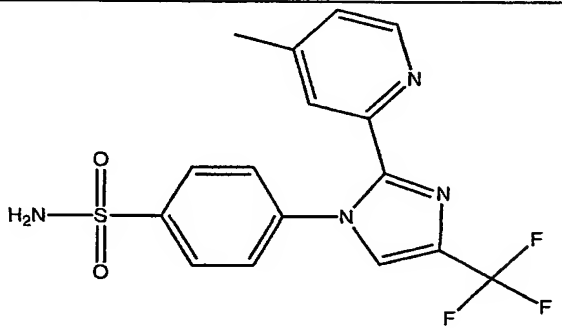
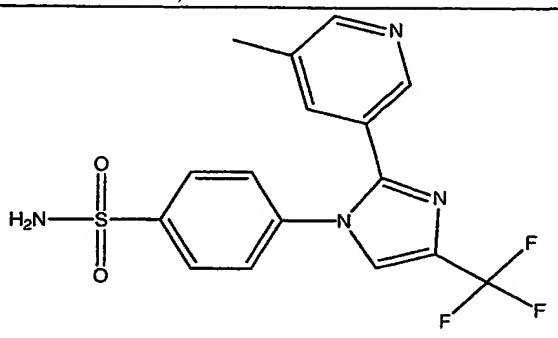
Compound Number	Structural Formula
B-112	 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
B-113	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
B-114	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

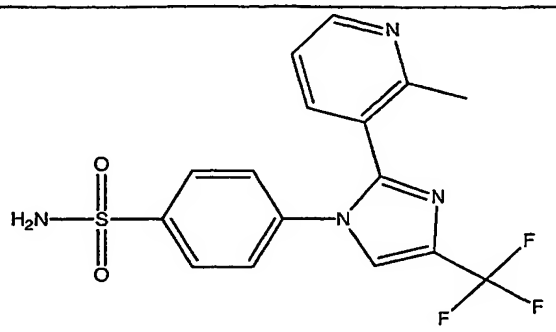
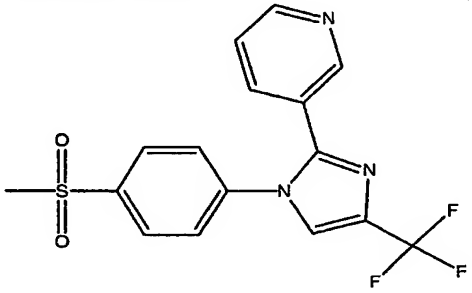
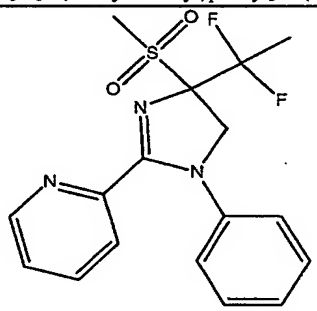
Compound Number	Structural Formula
B-115	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
B-116	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
B-117	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

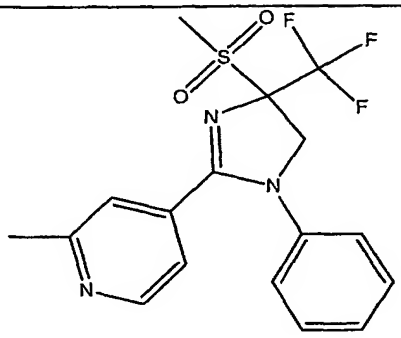
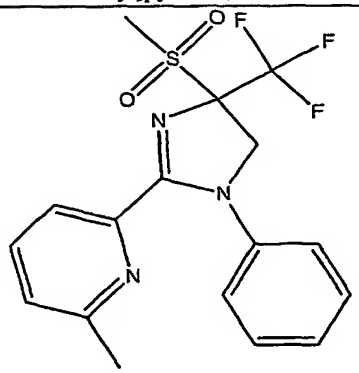
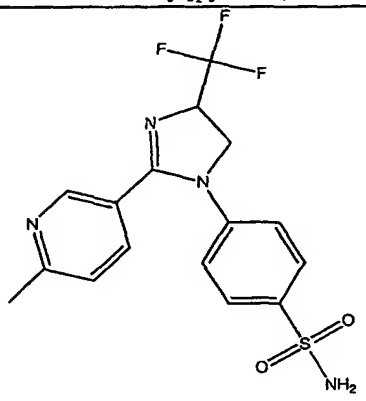
Compound Number	Structural Formula
B-118	 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;
B-119	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
B-120	 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl) cyclopenta-2,4-dien-3-yl]benzene;

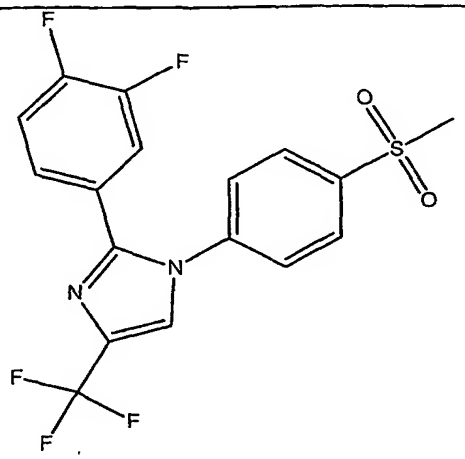
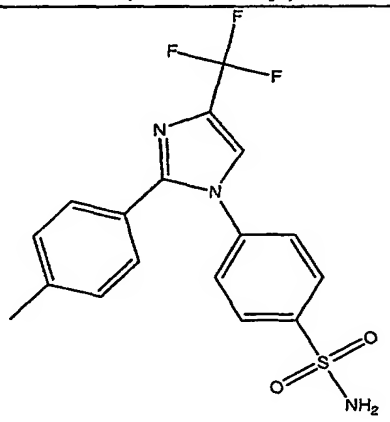
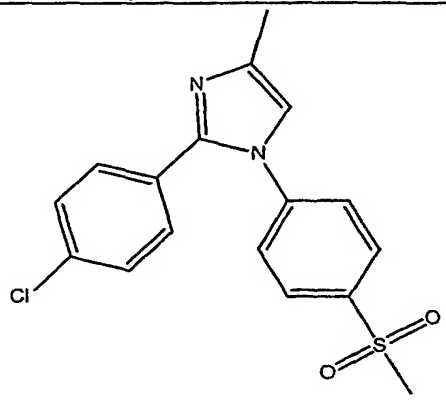
Compound Number	Structural Formula
B-121	 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide;
B-122	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
B-123	 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

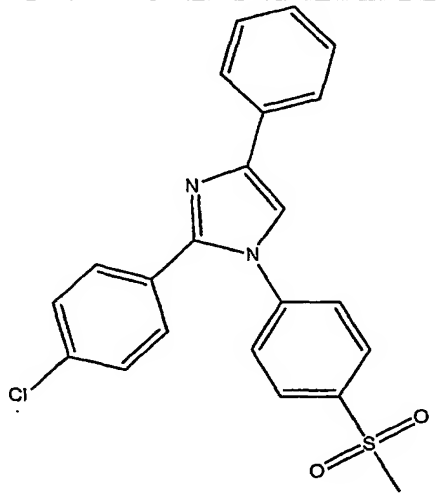
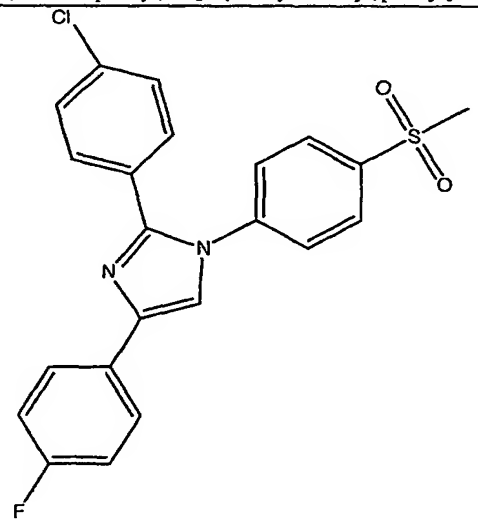
Compound Number	Structural Formula
B-124	 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;
B-125	 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;

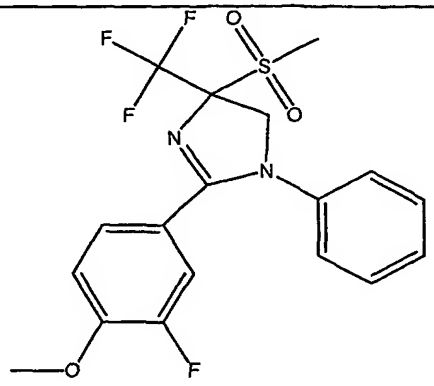
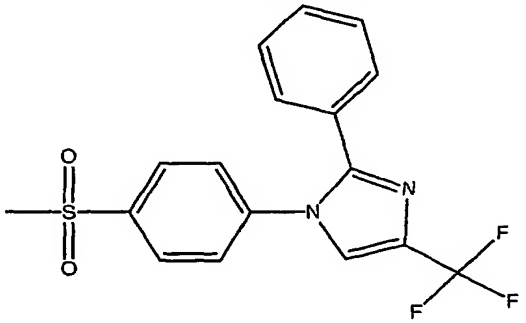
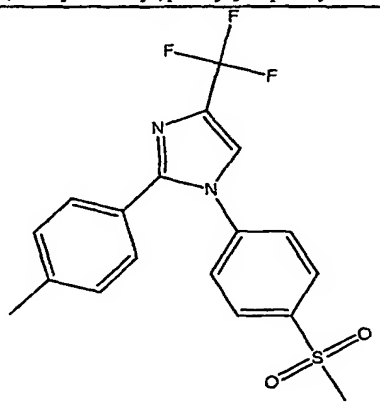
Compound Number	Structural Formula
B-126	 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;
B-127	 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-128	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;

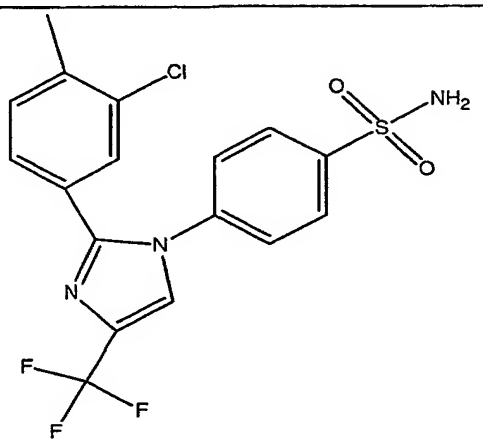
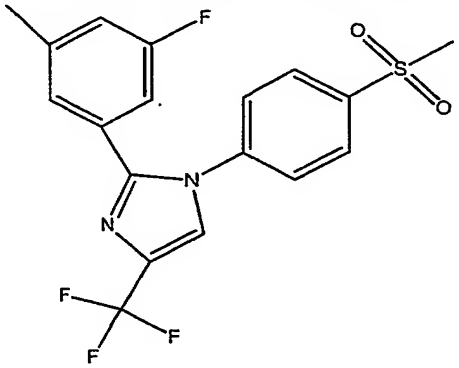
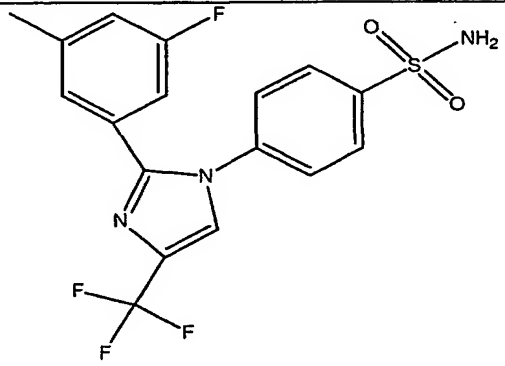
Compound Number	Structural Formula
B-129	 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-130	 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
B-131	 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;

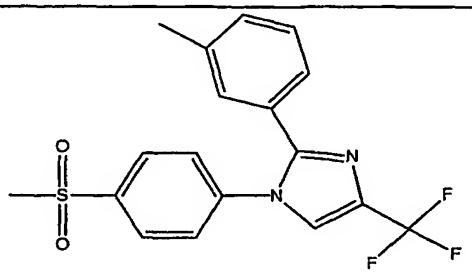
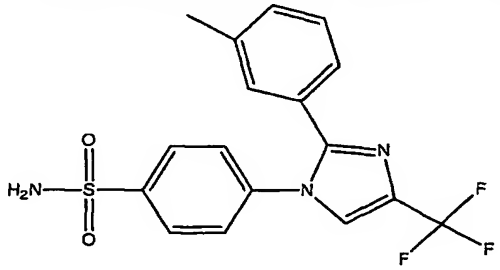
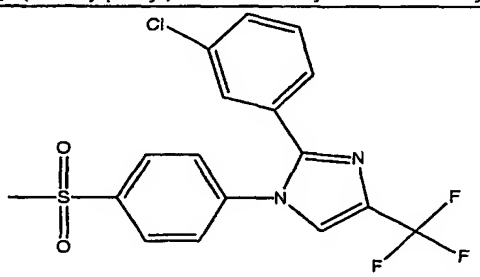
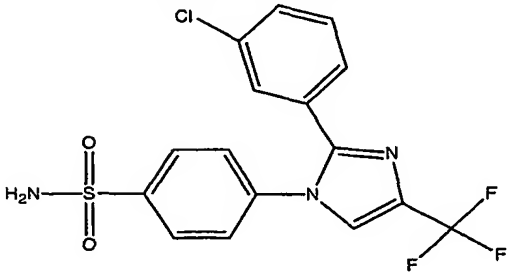
Compound Number	Structural Formula
B-132	 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;
B-133	 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;
B-134	 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

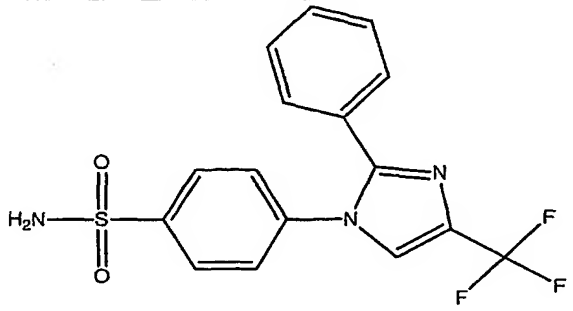
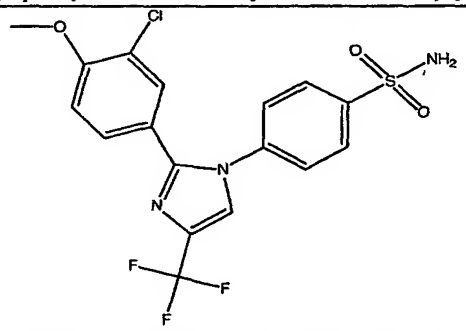
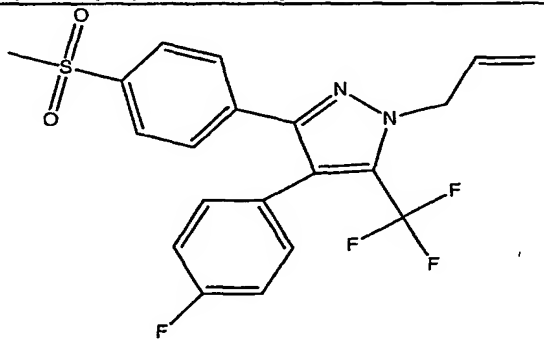
Compound Number	Structural Formula
B-135	 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;
B-136	 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-137	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

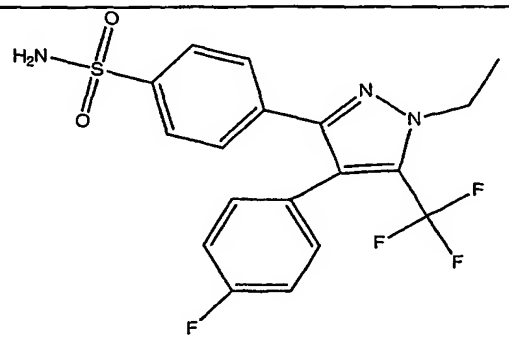
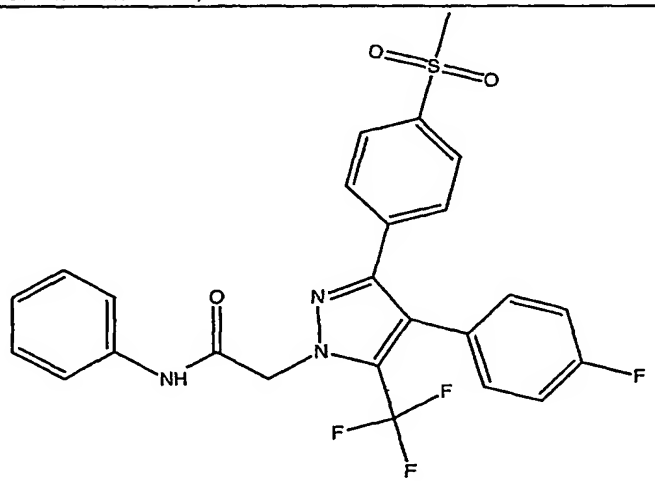
Compound Number	Structural Formula
B-138	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
B-139	 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl] -1H-imidazole;

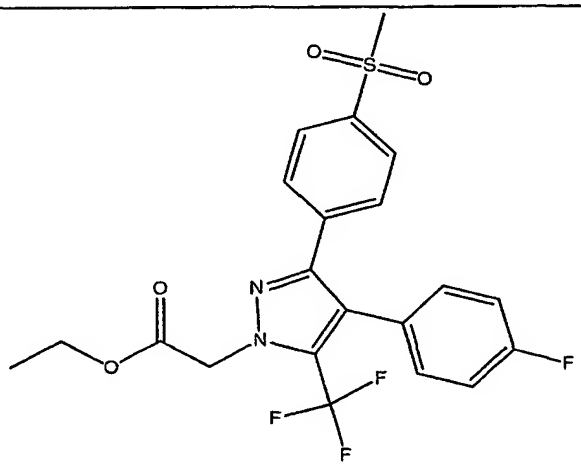
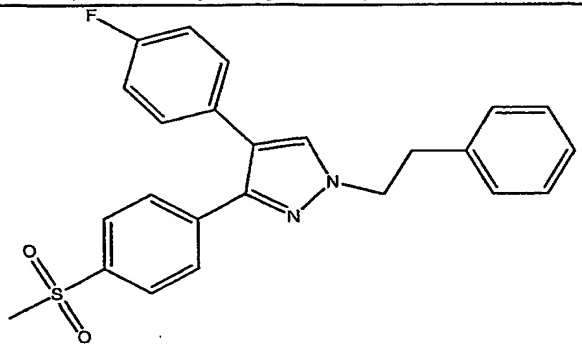
Compound Number	Structural Formula
B-140	 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl -4-(trifluoromethyl)]-1H-imidazole;
B-141	 *1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;*
B-142	 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

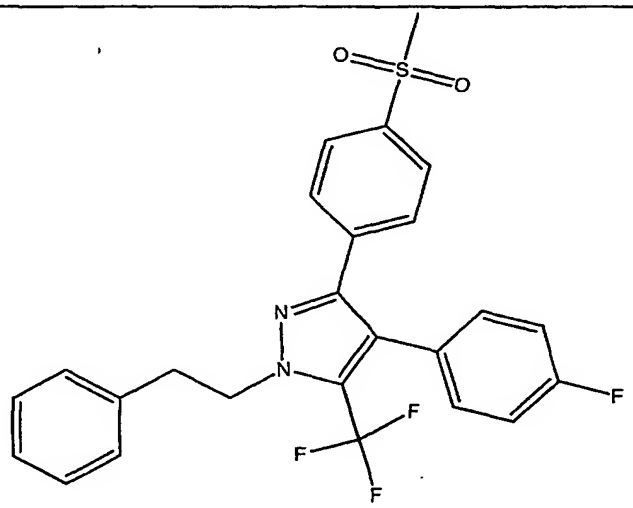
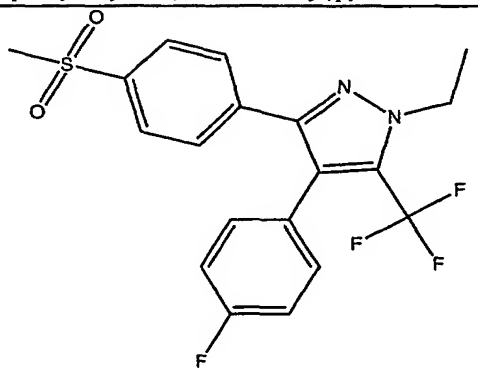
Compound Number	Structural Formula
B-143	 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-144	 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;
B-145	 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl -1H-imidazole-1-yl]benzenesulfonamide;

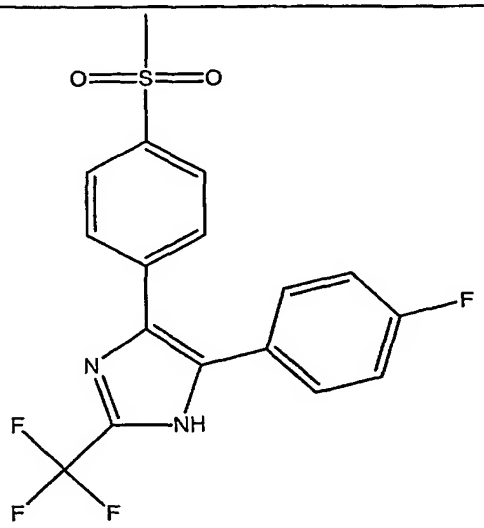
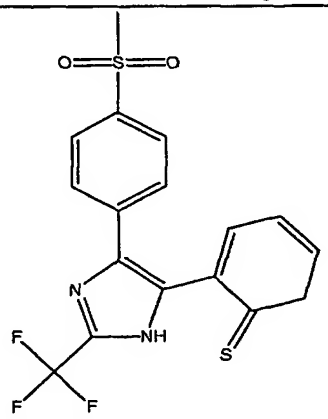
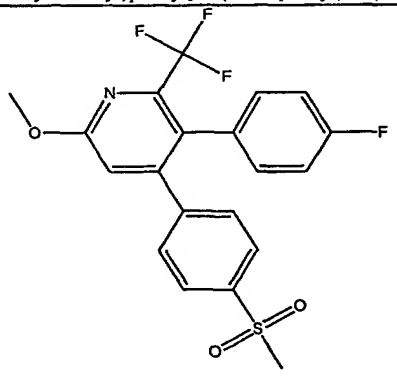
Compound Number	Structural Formula
B-146	 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
B-147	 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-148	 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole
B-149	 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

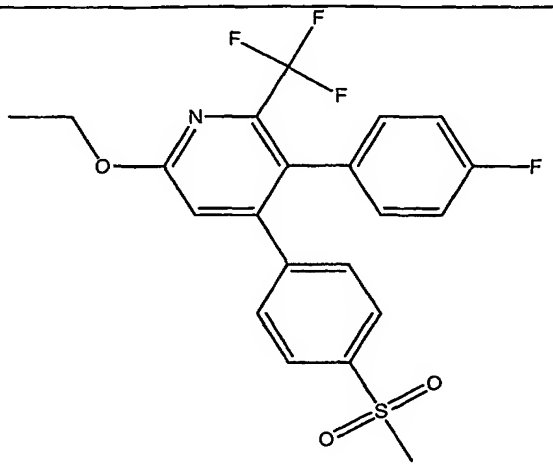
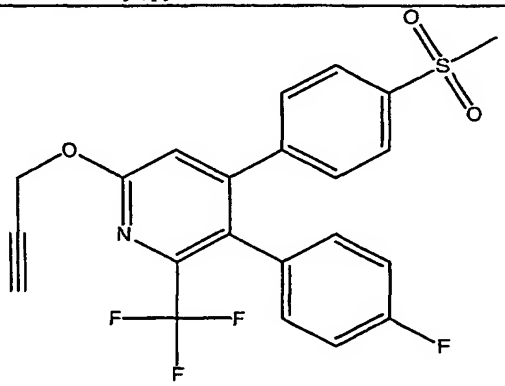
Compound Number	Structural Formula
B-150	 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-151	 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-152	 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

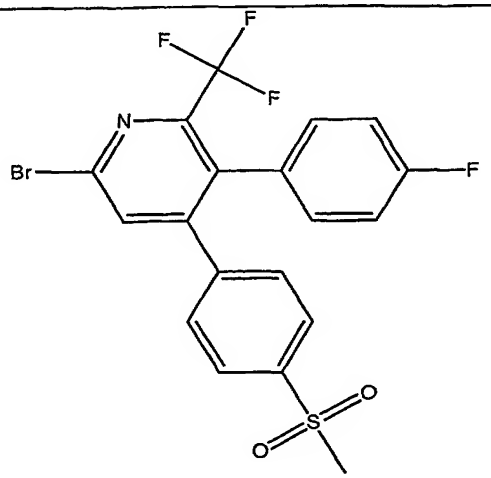
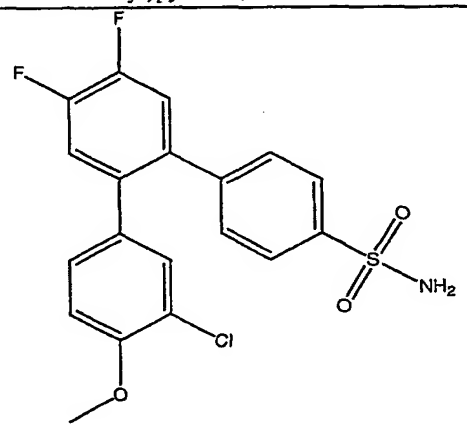
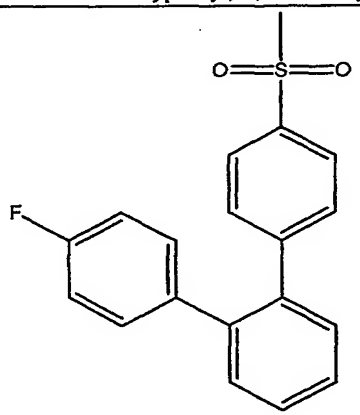
Compound Number	Structural Formula
B-153	 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide;
B-154	 N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

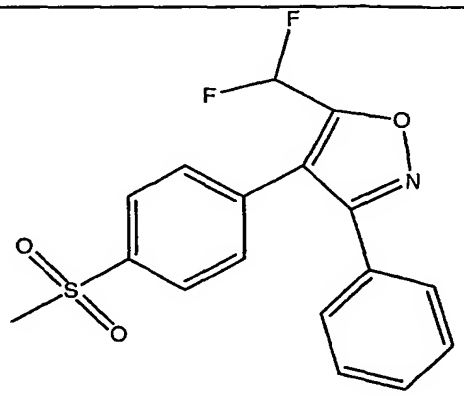
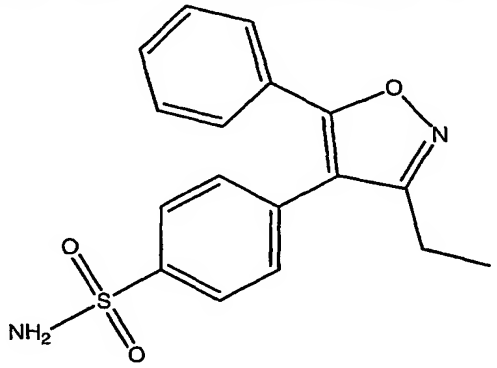
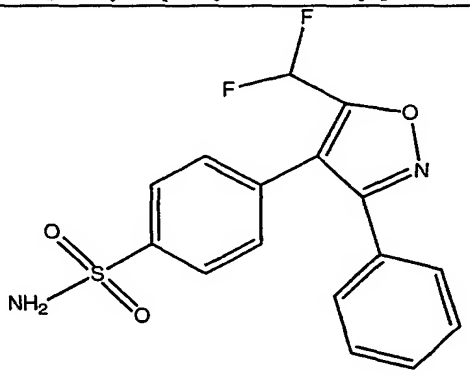
Compound Number	Structural Formula
B-155	 ethyl[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
B-156	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

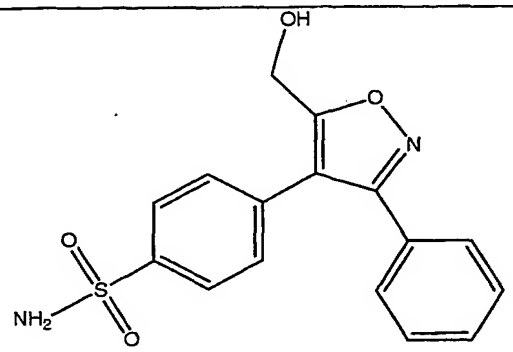
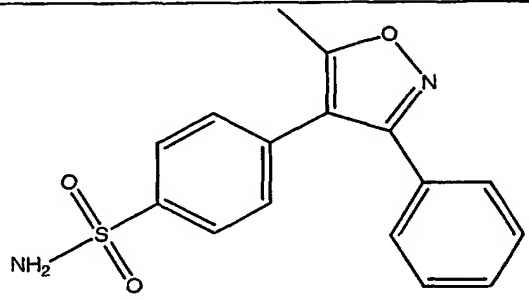
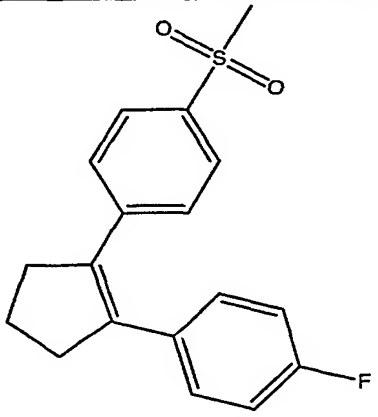
Compound Number	Structural Formula
B-157	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
B-158	 1-ethyl-4-(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

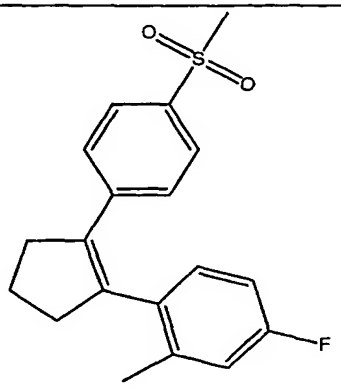
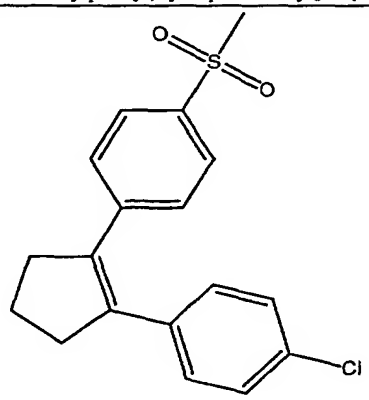
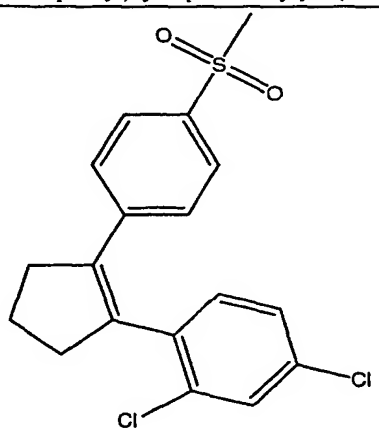
Compound Number	Structural Formula
B-159	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl) -2-trifluoromethyl-1H-imidazole;
B-160	 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
B-161	 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

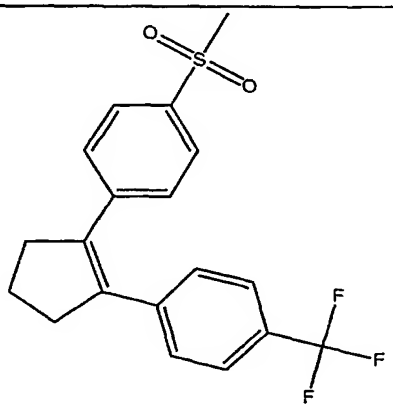
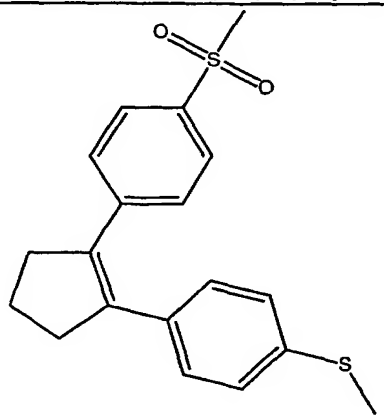
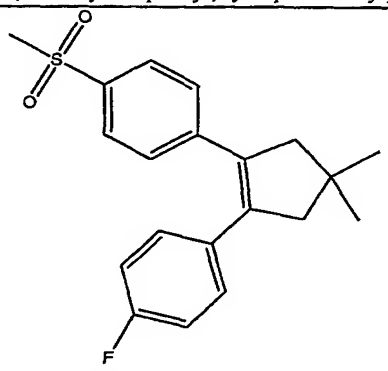
Compound Number	Structural Formula
B-162	 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;
B-163	 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

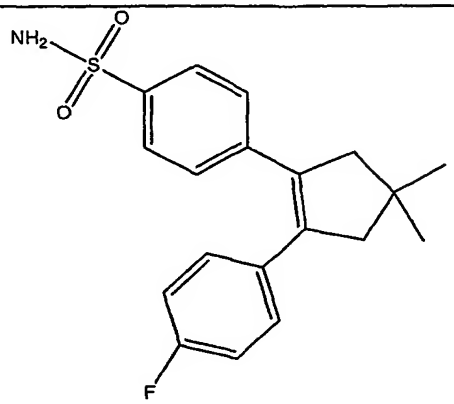
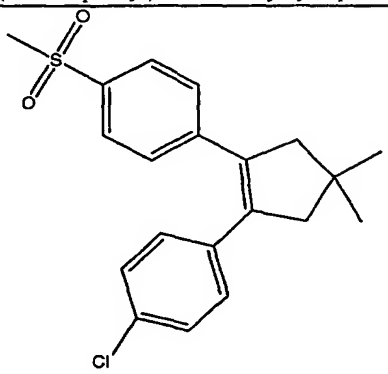
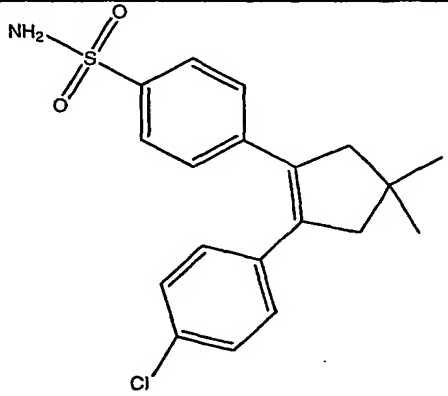
Compound Number	Structural Formula
B-164	 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;
B-165	 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
B-166	 1-(4-fluorophenyl)-2-[4-methylsulfonyl)phenyl]benzene;

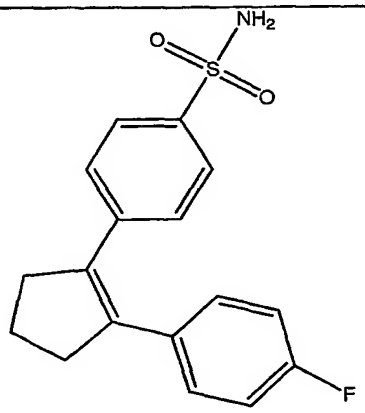
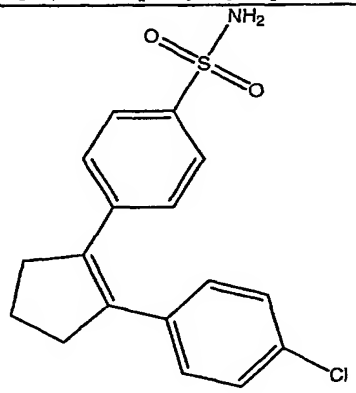
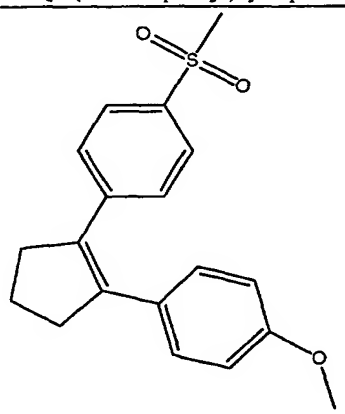
Compound Number	Structural Formula
B-167	 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;
B-168	 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
B-169	 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

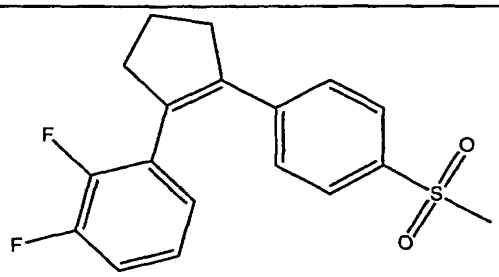
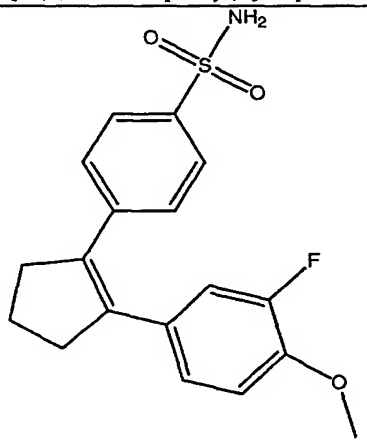
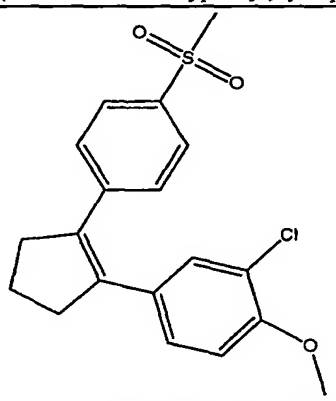
Compound Number	Structural Formula
B-170	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-171	 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
B-172	 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

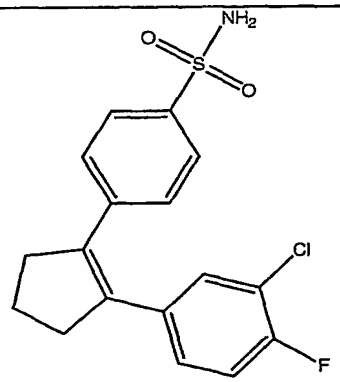
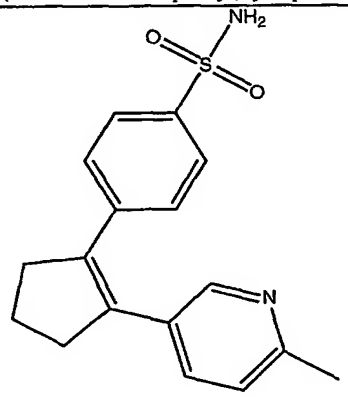
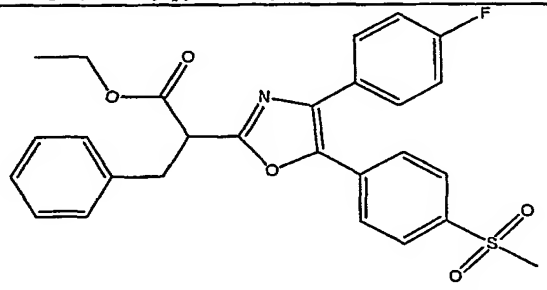
Compound Number	Structural Formula
B-173	 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-174	 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-175	 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

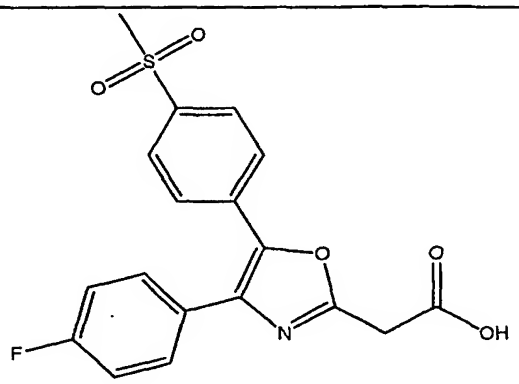
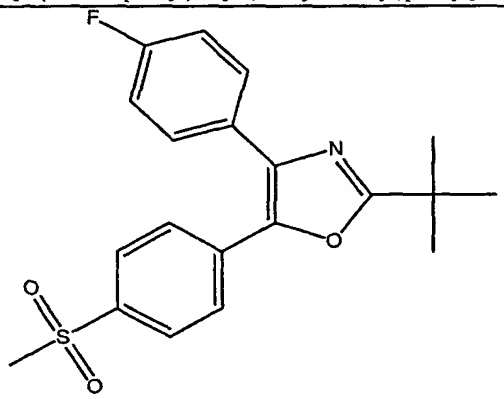
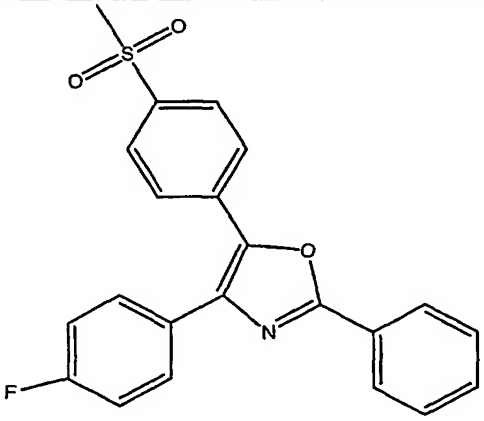
Compound Number	Structural Formula
B-176	 1-[2-(4-trifloromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-177	 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-178	 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

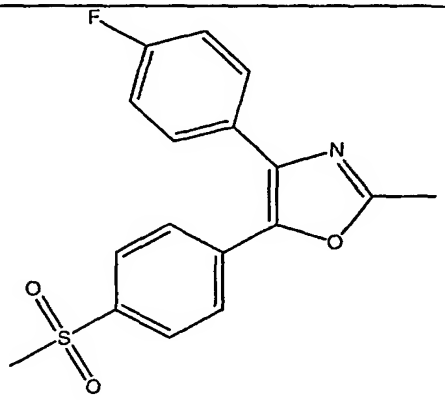
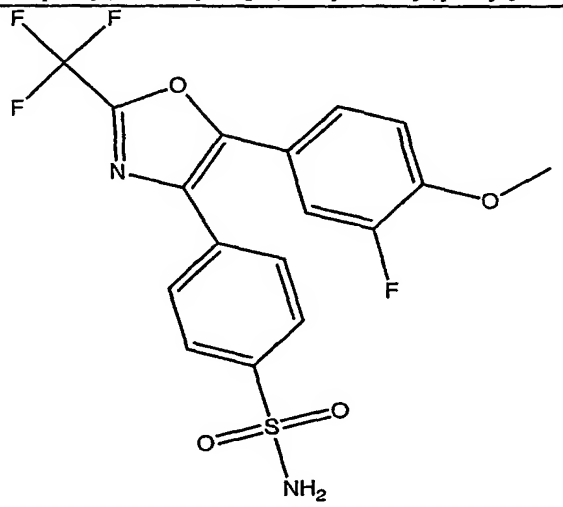
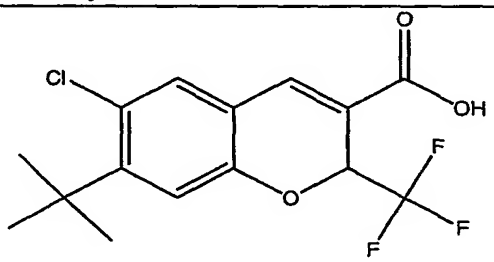
Compound Number	Structural Formula
B-179	 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
B-180	 1-[2-(3-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-181	 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

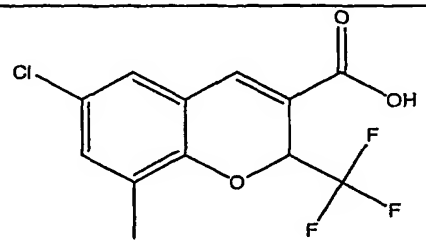
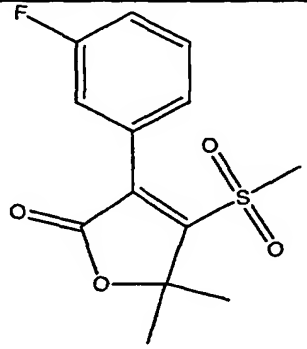
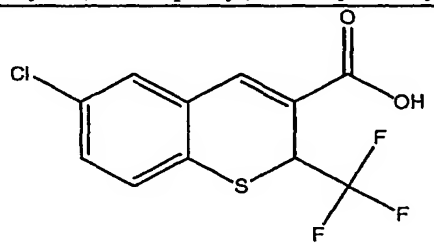
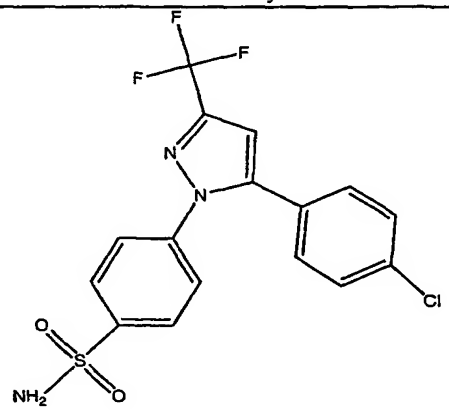
Compound Number	Structural Formula
B-182	 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-183	 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-184	 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

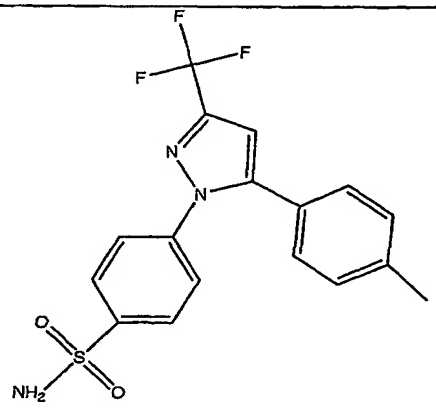
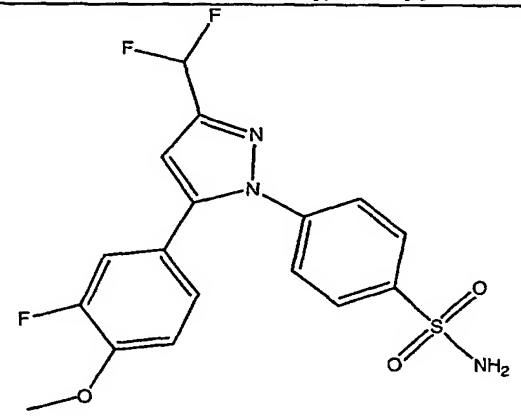
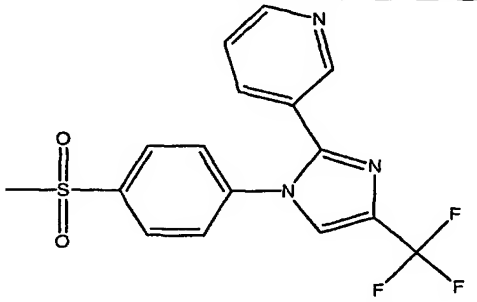
Compound Number	Structural Formula
B-185	 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-186	 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
B-187	 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

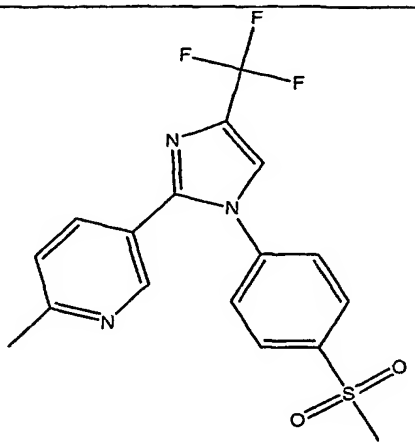
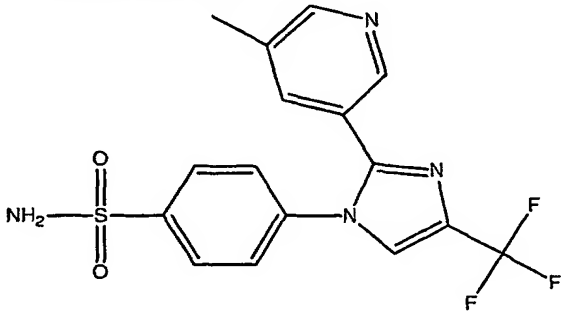
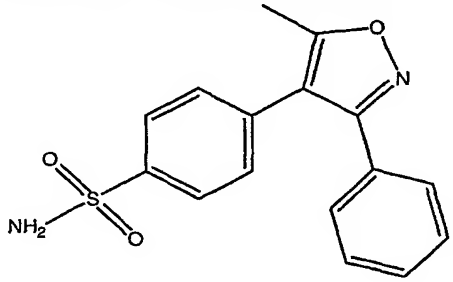
Compound Number	Structural Formula
B-188	 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-189	 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
B-190	 ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;

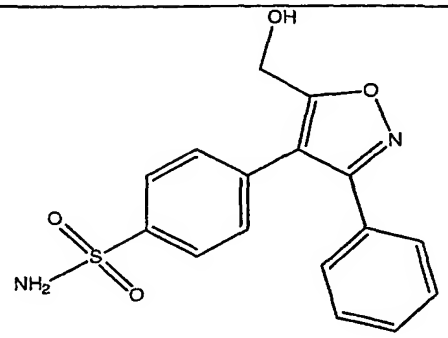
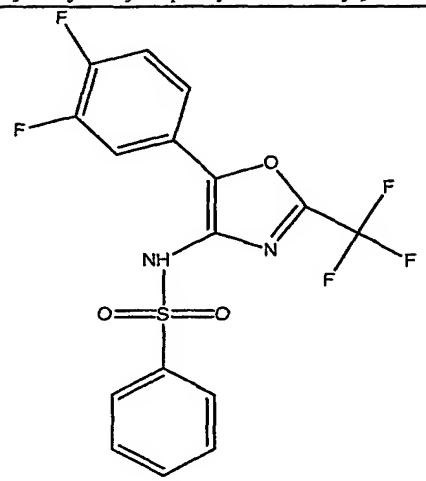
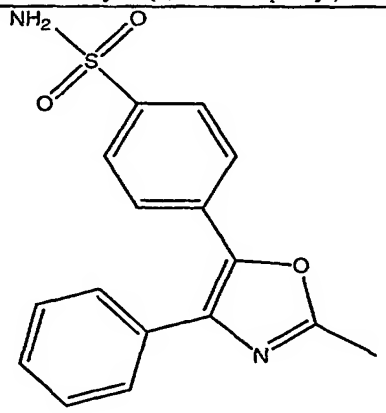
Compound Number	Structural Formula
B-191	 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;
B-192	 2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
B-193	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

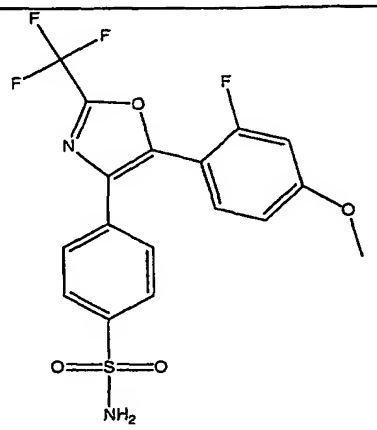
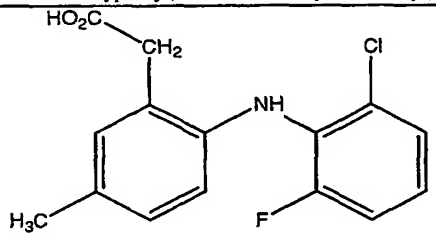
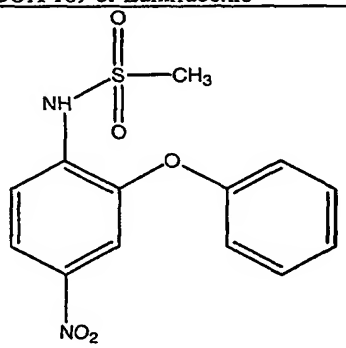
Compound Number	Structural Formula
B-194	 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
B-195	 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl -4-oxazolyl]benzenesulfonamide;
B-196	 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H -1-benzopyran-3-carboxylic acid;

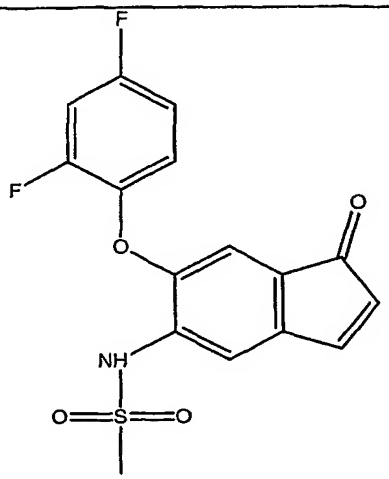
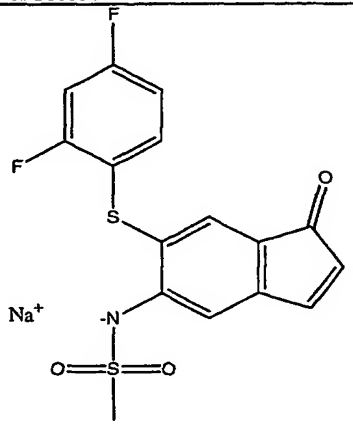
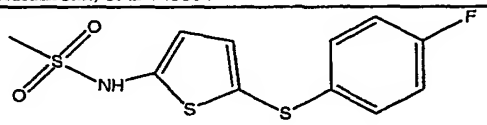
Compound Number	Structural Formula
B-197	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-198	 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone;
B-199	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
B-200	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

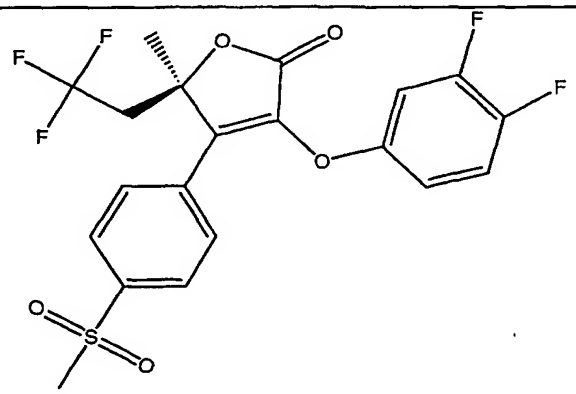
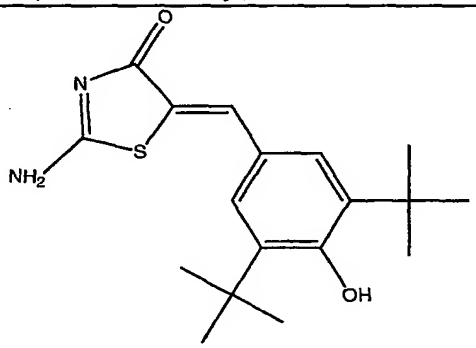
Compound Number	Structural Formula
B-201	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-202	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;
B-203	 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

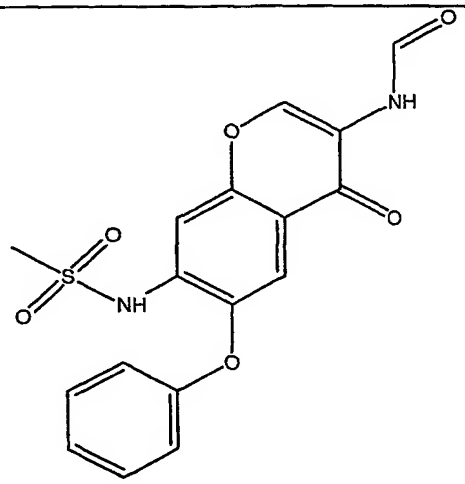
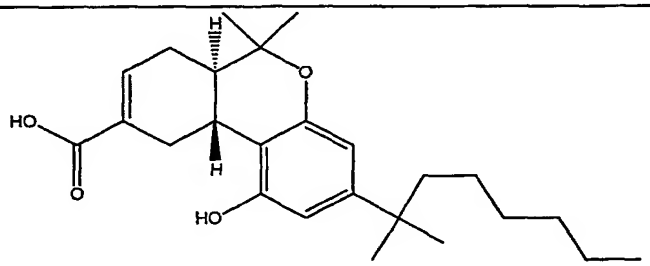
Compound Number	Structural Formula
B-204	 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl -1H-imidazol-2-yl]pyridine;
B-205	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-206	 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

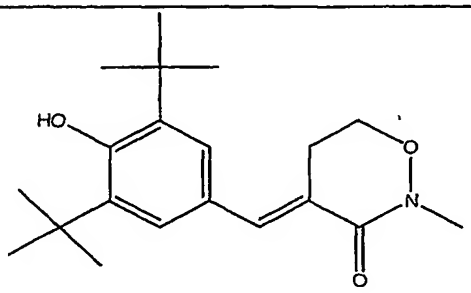
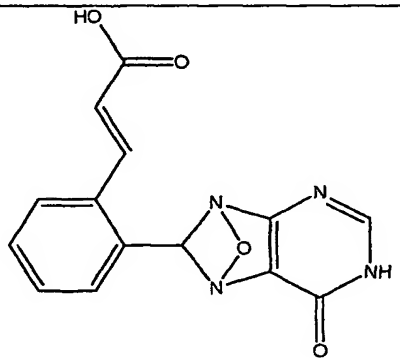
Compound Number	Structural Formula
B-207	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-208	 [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
B-209	 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;

Compound Number	Structural Formula
B-210	 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
B-211	 [2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid or COX 189 or Lumiracoxib
B-212	 *N*-(4-nitro-2-phenoxy-phenyl)-methanesulfonamide or Nimesulide

Compound Number	Structural Formula
B-213	 N-[6-(2,4-difluoro-phenoxy)-1-oxo-inden-5-yl]-methanesulfonamide or Flosulide
B-214	 *N*-[6-(2,4-difluoro-phenylsulfanyl)-1-oxo-1*H*-inden-5-yl]-methanesulfonamide, soldium salt, or L-745337
B-215	 N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide or RWJ-63556

Compound Number	Structural Formula
B-216	 3-(3,4-difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl -5-(2,2,2-trifluoro-ethyl)-5*H*-furan-2-one or L-784512
B-217	 (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] -4(5H)-thiazolone or Darbufelone
B-218	CS-502
B-219	LAS-34475
B-220	LAS-34555
B-221	S-33516
B-222	SD-8381
B-223	L-783003

Compound Number	Structural Formula
B-224	 N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] -methanesulfonamide or T614
B-225	D-1367
B-226	L-748731
B-227	 (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethy l-6H-dibenzo[b,d]pyran-9-carboxylic acid or CT3
B-228	CGP-28238

Compound Number	Structural Formula
B-229	 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389
B-230	GR-253035
B-231	 2-(6-dioxo-9H-purin-8-yl)cinnamic acid
B-232	S-2474

The compounds utilized in the methods of the present invention may be in the form of free bases or pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt may vary, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds for use in the present methods may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of

organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of use in the present methods include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound of any Formula set forth herein.

The cyclooxygenase-2 selective inhibitors useful in the practice of the present methods can be formulated into pharmaceutical compositions and administered by any means that will deliver a therapeutically effective dose. Such compositions can be administered orally, parenterally, by inhalation spray, rectally, intradermally, transdermally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania (1975), and Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y. (1980).

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils

are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the compounds discussed herein can be prepared by mixing the active agent with a suitable non-irritating excipient such as cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature, and which will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form will vary depending upon the patient and the particular mode of administration. In general, the pharmaceutical compositions may contain a cyclooxygenase-2 selective inhibitor in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 200 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably from about 1 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

In one embodiment, when the cyclooxygenase-2 selective inhibitor comprises rofecoxib, it is preferred that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more preferably from about 0.18 to about 0.4 mg/day·kg.

In still another embodiment, when the cyclooxygenase-2 selective inhibitor comprises etoricoxib, it is preferred that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more preferably from about 0.8 to about 4 mg/day·kg.

Further, when the cyclooxygenase-2 selective inhibitor comprises celecoxib, it is preferred that the amount used is within a range of from about 1 to about 20 mg/day·kg, even more preferably from about 1.4 to about 8.6 mg/day·kg, and yet more preferably from about 2 to about 3 mg/day·kg.

When the cyclooxygenase-2 selective inhibitor comprises valdecoxib, it is preferred that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more preferably from about 0.8 to about 4 mg/day·kg.

In a further embodiment, when the cyclooxygenase-2 selective inhibitor comprises parecoxib, it is preferred that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more preferably from about 1 to about 3 mg/day·kg.

Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics,

Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

In another embodiment, the pharmaceutical composition containing a suitable cyclooxygenase-2 selective inhibitor can also be administered locally at the site of vascular injury. For example and without limitation, a cyclooxygenase-2 selective inhibitor can be incorporated into a stent to be implanted into the vasculature. The stent can be coated with a degradable polymer into which the cyclooxygenase-2 selective inhibitor has been incorporated. As the polymer slowly degrades, it would release the cyclooxygenase-2 selective inhibitor into the area surrounding the stent. An example of a stent coated with a degradable polymer can be found in Strecker et al. (*Cardiovasc. Intervent. Radiol.*, 21:487-496, 1998). Alternatively, local administration can be achieved by the use of microspheres that are implanted into the vascular wall at the time of vascular intervention. An example of the use of microspheres for administration of compounds to the vascular wall can be found in Valero et al. (*J. Cardiovasc. Pharmacol.* 31:513-519, 1998). Also included are catheter-based local delivery systems. Non-limiting examples of catheter-based local delivery systems include hydrophilic-coated catheter balloons that absorb the cyclooxygenase-2 selective inhibitor and then release it when pressed against the vessel wall, and fenestrated balloon catheters that use a high velocity jet to spray the cyclooxygenase-2 selective inhibitor against the vessel wall and thus embed it in the vessel wall.

The timing of the administration of the cyclooxygenase-2 selective inhibitor can also vary. For example, the cyclooxygenase-2 selective inhibitor can be administered beginning at a time prior to vascular intervention, at the time of vascular intervention, or at a time after vascular intervention. Administration can be by a single dose, or more preferably the cyclooxygenase-2 selective inhibitor is given over an extended period. In one embodiment, administration of the cyclooxygenase-2 selective inhibitor is commenced at one day prior to vascular intervention. In other embodiments, the cyclooxygenase-2 selective inhibitor is given beginning not more than 7, not more than 14, not more than 21, or not more that 30 days prior to the vascular intervention. It is preferred that administration of the cyclooxygenase-2 selective inhibitor extend for a period after the vascular intervention. In one embodiment, administration is continued for six months following intervention. In other embodiments, administration of the cyclooxygenase-2 selective inhibitor is continued for 1 week, 2 weeks, 1 month, 3

months, 9 months, or one year after vascular intervention. In one embodiment, administration of a cyclooxygenase-2 selective inhibitor is continued throughout the life of the subject following vascular intervention.

In the present method, the cyclooxygenase-2 selective inhibitor is administered in combination with radiation. The timing of the administration of the cyclooxygenase-2 selective inhibitor and radiation may vary from subject to subject. In one embodiment of the invention, the cyclooxygenase-2 selective inhibitor and radiation may be administered substantially simultaneously, meaning that both agents may be administered to the subject at approximately the same time. In one embodiment, for example, the cyclooxygenase-2 selective inhibitor or pharmaceutically acceptable salt or prodrug thereof is administered during a continuous period beginning on the same day as the beginning of the radiation therapy and extending to a period after the end of the radiation therapy. Alternatively, the cyclooxygenase-2 selective inhibitor and radiation may be administered sequentially, meaning that they are administered at separate times during separate treatments. In one embodiment, for example, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is administered during a continuous period beginning prior to administration of the radiation and ending after administration of the radiation. Of course, it is also possible that the cyclooxygenase-2 selective inhibitor may be administered either more or less frequently than the radiation treatment. One skilled in the art can readily design suitable treatment regiments for a particular subject.

It will be apparent to those skilled in the art that it is possible, and perhaps desirable, to combine various times and methods of administration in the practice of the present invention. For example and without limitation, a subject may be administered a cyclooxygenase-2 selective inhibitor systemically for a period prior to the vascular procedure, followed by local administration by, for example, a cyclooxygenase-2 selective inhibitor releasing stent, followed by radiation treatment, followed by systemic administration after the release of the cyclooxygenase-2 selective inhibitor stops or has a significant decline.

The exact dose of radiation used will also vary with such factors as the tissue location, the species, age, sex and physical condition of the subject, the size of the tissue, and the type of vascular intervention involved. Exemplary radiation doses for coronary artery procedures are in the range of between about 3 Grays (Gy) to 60 Grays. In one

embodiment the dose is between about 8 Gy to about 35 Gy, in another embodiment between about 10 Gy to about 24 Gy and in still another embodiment between about between about 12 Gy to about 20 Gy.

Generally speaking, the radiation may be administered to any portion of a subject's body to the extent that its delivery to the location results in the desired degree of cell proliferation inhibition. Typically, the radiation is directed to a coronary blood vessel. In one embodiment, the coronary blood vessel is a coronary artery.

The radiation may be administered according to any method generally known in the art. In one embodiment, a platform is used to administer the radiation. The platform can be external, for example, a linear accelerator, or may be endovascular brachytherapy using, for example, a catheter or radioactive stent. One method of endovascular radiation therapy makes use of commercially available high dose rate after-loader systems. Another method utilizes catheters and in particular balloon catheters. The catheters may contain a solid radiation source or a liquid source. In catheter-based systems, the catheter is advanced to the site to be irradiated and the balloon expanded to come in contact with the vessel walls. In an alternative embodiment, an implantable radiation source is used. Implantable radiation sources include, but are not limited to, radioactive stents, particles and microspheres. When ultra violet (UV) radiation is utilized, an optical fiber or other wave-guide can be used. Examples of methods for endovascular brachytherapy can be found in Massullo et al. (*Intl. J. Radiation Oncol. Biol. Phys.*, 36:973-975, 1996); Teirstein et al. (*N. E. J. Med.*, 336:1697-1703, 1997); Valero et al. (*J. Cardiovasc. Pharmacol.*, 31:513-519; 1998); Ishiwata et al. (*Jpn Heart J.*, 41:541-570, 2000); and U.S. Patent numbers 5,662,580; 5,871,437; 5,919,126; 5,919,126; 6,159,142; 6,179,789; 6,187,037; 6,196,963; 6,196,996; 6,200,256; and 6,210,313. Examples of methods for the administration of UV radiation can be found in U.S. Patent numbers 5,116,864; 5,620,438; and 6,200,307.

Any type of radiation capable of inhibiting or preventing intimal hyperplasia can be used. In one embodiment, either electromagnetic or particle radiation can be used. Examples of suitable types of radiation include alpha particles, beta particles, gamma rays, X-rays and ultra violet radiation. One preferred form of X-rays is "soft X-rays" or Grenz rays. These X-rays are of a longer wavelength and thus less penetrating than those conventionally used in radiotherapy.

Numerous sources of radiation can also be used including antimony-120, antimony-127, astatine-211, barium-128, barium-131, barium-140, bromine-80m, cadmium-115, cerium-134, cerium-141, cerium-143, cobalt-55, copper-64, copper-67, dysprosium-166, erbium-169, erbium-172, holmium-166, gadolinium-159, gallium-166, gallium-68, germanium-71, gold-198, gold-199, iodine-124, iodine-125, iodine-131, iridium-192, iridium-194, lanthanum-140, lutetium-172, lutetium-177, neodymium-140, nickel-66, niobium-95, osmium-191, palladium-100, palladium-103, phosphorus-32, phosphorus-33, platinum-188, platinum-191, platinum-193m, platinum-195m, platinum-197, praseodymium-143, rhenium-186, rhenium-188, rhodium-99, rhodium-101m, rhodium 103m, rhodium-105, rubidium-82, ruthenium-103, samarium-153, scandium-47, scandium-48, silver-111, strontium-82, strontium-89, strontium-90, tantalum-177, tantalum-183, technetium-99m, tellurium-132, tellurium-118, terbium-153, terbium-156, thallium-201, thallium-204, thulium-170, thulium-172, tin-117m, tin-121, titanium-45, tungsten-178, vanadium-48, xenon-133, ytterbium-166, ytterbium-169, ytterbium-175, yttrium-87, yttrium-90, yttrium-91, zinc-72, and zirconium-89. Commonly used sources of radiation can be found in Table 3. As will be apparent to those skilled in the art, sources of radiation can be combined as, for example, a combination of strontium-90 and yttrium-90 ($^{90}SR/^{90}Y$).

Table 4

Commonly Used Radiation Sources for Vascular Brachytherapy

ISOTOPE	EMISSION	MAX. ENERGY	HALF-LIFE
Iridium-192	Gamma, Beta	0.37 MeV	73.8 days
Strontium-90/ Yttrium-90	Beta	2.3 MeV	29.2 years
Yttrium-90	Beta	2.3 MeV	64.1 hours
Phosphorus-32	Beta	1.71 MeV	14.3 days
Rhenium-188	Beta, Gamma	2.12 MeV	17 hours
Rhenium-186	Beta	1.08 MeV	90 hours
Xenon-133	Beta, Gamma, X-ray	360, 81, 32 keV	5.3 days
Technetium-99m	Beta, X-ray	0.14 MeV	6 hours

In one embodiment, the method will further involve the administration of an antithrombotic agent and/or a platelet aggregation inhibitor. The administration of the antithrombotic agent or platelet aggregation inhibitor will typically begin prior to the vascular intervention and will extend for a period afterward, often the life of the subject. Protocols for the administration of antithrombotics and platelet aggregation inhibitors for use in vascular intervention and coronary artery intervention in particular is widely available.

In another embodiment, the methods will further comprise administration of a corticosteroid, preferably a glucocorticoid. Examples of suitable glucocorticoids include hydrocortisone, dexamethasone and methylpridnisolone.

Examples

The following examples are intended to provide illustrations of the application of the present invention. The following examples are not intended to completely define or otherwise limit the scope of the invention.

Example 1

Animal Models for Restenosis

Various animal models have been developed to study cardiovascular disease in general and restenosis in particular. Reviews of these models can be found in Herrman et al. (*Drugs*, 46:18-52, 1993) and Landzberg et al. (*Prog. Cardiovasc. Dis.*, 39:361-398, 1997). One of the most widely used models, is the balloon-injured swine restenosis model of Karas et al. (*J. Am. Coll. Cardiol.*, 20:467-474, 1992). In this method, coronary anteriography is performed on anesthetized domestic swine using a guiding catheter introduced into the femoral artery. Coronary vessel diameter is estimated from the arteriograms using catheter diameter as a standard. In order to induce vascular injury, balloons typically used have a diameter approximately 20% to 30% greater than the baseline arterial diameter. If a stent is to be implanted, the balloon is normally inflated twice for 30 seconds and then the catheter is removed. If the vessel is to remain unstented, the balloon is usually inflated three times. The site of balloon inflation and/or stenting can be irradiated immediately before, during or after the angioplasty. Various doses of radiation can be used in order to determine the optimal dose. Typically, radiation doses will be in the range of between about 3 Grays to about 60 Grays, more

typically in the range of about 10 Grays to 24 Grays and even more typically in the range of about between 12 Grays to 20 Grays. The dose of radiation is administered using any suitable method. Often radiation is administered using the same catheter used to expand the vessel. If UV radiation is used, an optical wave-guide is inserted through the femoral artery and area of expansion treated with UV light. Following the procedure, the cutdown wound used to introduce the catheter is repaired and the animal allowed to recover.

To test the effect of administration of cyclooxygenase-2 selective inhibitors in combination with radiation to prevent restenosis, cyclooxygenase-2 selective inhibitors are administered at various doses and at various times prior to and after vascular intervention. The exact range of doses tested will vary with the particular cyclooxygenase-2 selective inhibitor to be tested. Any suitable method of administration can be used, for example, animals can be administered the compound orally from one to four times a day. The time period of administration is also varied to determine the optimal duration of administration. Typically, administration of the cyclooxygenase-2 selective inhibitor will begin shortly before or at the time of the vascular intervention and extend for varying periods after. Administration of cyclooxygenase-2 selective inhibitor throughout the course of the study is contemplated. The exact length of time of the study will vary with the particular situation, but in general, it is anticipated that studies will last from between 1 to 6 months.

Example 2

Analysis of Effect of Combination Therapy on Restenosis

At various times during the course of the study, the effect of the combination therapy on restenosis can be assessed. On method of assessment is by histological study. At various times, animals from treatment and control groups are sacrificed and the treated vessels quickly removed and fixed. The control group consists of animals that underwent the vascular intervention but did not receive the combination of cyclooxygenase-2 selective inhibitor and radiation. Fixed vessels are then embedded in a suitable sectioning material, sectioned, stained and examined by either light or electron microscopy. Vessel sections can be examined for known parameters associated with restenosis such as the size of the vessel lumen and the number of smooth muscle cells present in the section.

Alternatively, the effects can be determined by the use of arteriography or intravascular ultrasound. These methods have the advantage in that individual animals can be followed during the course of the study and data from various time points compared. Animals are anesthetized and anteriography or intravascular ultrasound performed in the same method as for angioplasty and the images recorded. A contrast filled catheter can be used for a calibration standard. Images obtained are then matched for position within the cardiac cycle and the diameters of the lumens compared. It is possible, of course, to combine both histological and arteriographic or ultrasound analysis, by measuring vessel diameter by arteriography or ultrasound during the experimental period and then sacrificing the animal at the end of the study in order to conduct a histological examination.

Example 3

Rat Carrageenan Foot Pad Edema Test

The anti-inflammatory properties of cyclooxygenase-2 selective inhibitors for use in the present methods can be determined by the rat carrageenan foot pad edema test. The carrageenan foot edema test is performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, 111: 544, 1962). Male Sprague-Dawley rats are selected in each group so that the average body weight is as close as possible. Rats are fasted with free access to water for over sixteen hours prior to the test. The rats are dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later, a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline is administered and the volume of the injected foot is measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot is again measured. The average foot swelling in a group of drug-treated animals is compared with that of a group of placebo-treated animals and the percentage inhibition of edema is determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs*, in *Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)).

In light of the detailed description of the invention and the examples presented above, it can be appreciated that the several aspects of the invention are achieved.

It is to be understood that the present invention has been described in detail by way of illustration and example in order to acquaint others skilled in the art with the invention, its principles, and its practical application. Particular formulations and processes of the present invention are not limited to the descriptions of the specific embodiments presented, but rather the descriptions and examples should be viewed in terms of the claims that follow and their equivalents. While some of the examples and descriptions above include some conclusions about the way the invention may function, the inventor does not intend to be bound by those conclusions and functions, but puts them forth only as possible explanations.

It is to be further understood that the specific embodiments of the present invention as set forth are not intended as being exhaustive or limiting of the invention, and that many alternatives, modifications, and variations will be apparent to those of ordinary skill in the art in light of the foregoing examples and detailed description. Accordingly, this invention is intended to embrace all such alternatives, modifications, and variations that fall within the spirit and scope of the following claims.

What is claimed is:

1. A method for the treatment or prevention of cardiovascular disease in a subject in need of such treatment, the method comprising administering to the subject a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof and a dose of radiation.

5

2. The method of claim 1, wherein the cardiovascular disease is characterized by at least one symptom selected from the group consisting of thrombosis, intimal hyperplasia, negative remodeling, and local inflammation.

3. The method of claim 1, wherein the cardiovascular disease is due to coronary vessel thrombosis.

4. The method of claim 1, wherein the cardiovascular disease is due coronary vessel intimal hyperplasia.

5. The method of claim 1, wherein the radiation is directed to a coronary blood vessel.

6. The method of claim 5, wherein the coronary blood vessel is a coronary artery.

7. The method of claim 1, wherein the radiation is administered by brachytherapy, direct beam radiation or a combination thereof.

8. The method of claim 1, where the radiation is administered by brachytherapy.

9. The method of claim 1, wherein the radiation is administered by direct beam radiation.

10. The method of claim 8, wherein the brachytherapy is administered by catherterization.

11. The method of claim 8, wherein the brachytherapy is administered by radioactive stent.

12. The method of claim 1, wherein the radiation is administered at a dose between about 3 Gray and about 60 Gray.

13. The method of claim 1, wherein the radiation is administered at a dose between about 8 Gray to about 35 Gray.

14. The method of claim 1, wherein the radiation is administered at a dose between about 10 Gray to about 25 Gray.

15. The method of claim 1, wherein the radiation is administered at a dose between about 12 Gray to about 20 Gray.

16. The method of claim 1, wherein the radiation comprises particle radiation.

17. The method of claim 1, wherein the radiation comprises electromagnetic radiation.

18. The method of claim 1, wherein the radiation is selected from the group consisting of alpha particles, beta particles, gamma rays, X-rays, ultra violet radiation, and any combination thereof.

19. The method of claim 1, wherein the radiation comprises Grenz rays.

20. The method of claim 1, wherein the radiation is from a source selected from the group consisting of antimony-120, antimony-127, astatine-211, barium-128, barium-131, barium-140, bromine-80m, cadmium-115, cerium-134, cerium-141, cerium-143, cobalt-55, copper-64, copper-67, dysprosium-166, erbium-169, erbium-172, holmium-166, gadolinium-159, gallium-166, gallium-68, germanium-71, gold-198, gold-199, iodine-124, iodine-125, iodine-131, iridium-192, iridium-194, lanthanum-140, lutetium-172, lutetium-177, neodymium-140, nickel-66, niobium-95, osmium-191, palladium-100, palladium-103, phosphorus-32, phosphorus-33, platinum-188, platinum-191, platinum-193m, platinum-195m, platinum-197, praseodymium-143,

rhenium-186, rhenium-188, rhodium-99, rhodium-101m, rhodium 103m, rhodium-105, rubidium-82, ruthenium-103, samarium-153, scandium-47, scandium-48, silver-111, strontium-82, strontium-89, strontium-90, tantalum-177, tantalum-183, technetium-99m, tellurium-132, tellurium-118, terbium-153, terbium-156, thallium-201, thallium-204, thulium-170, thulium-172, tin-117m, tin-121, titanium-45, tungsten-178, vanadium-48, xenon-133, ytterbium-166, ytterbium-169, ytterbium-175, yttrium-87, yttrium-90, yttrium-91, zinc-72, and zirconium-89; and any combination thereof.

21. The method of claim 1, wherein the radiation is from a source selected from the group consisting of Iridium-192, Strontium-90, Phosphorus-32, Rhenium-186, Rhenium-188, Xenon-133, and Technetium-99m; and any combination thereof.

22. The method of claim 1, wherein the radiation is from Iridium-192.

23. The method of claim 1, wherein the radiation is from Strontium-90.

24. The method of claim 1, wherein the radiation is from Phosphorus-32.

25. The method of claim 1, wherein the radiation is from Rhenium-186.

26. The method of claim 1, wherein the radiation is from Rhenium-188.

27. The method of claim 1, wherein the radiation is from Xenon-133.

28. The method of claim 1, wherein the radiation is from Technetium-99m.

29. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is administered during a continuous period beginning prior to administration of the radiation.

30. The method of claim 29, wherein administration of the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is continued until about six months after vascular intervention.

31. The method of claim 29, wherein administration of the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is continued for the life of the subject.

32. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor or pharmaceutically acceptable salt or prodrug thereof is administered during a continuous period beginning on the same day as the beginning of the radiation.

33. The method of claim 32, wherein administration of the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is continued until about six months after vascular intervention.

34. The method of claim 32, wherein administration of the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is continued for the life of the subject.

35. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor or pharmaceutically acceptable salt or prodrug thereof is administered during a continuous period beginning after the administration of the radiation.

36. The method of claim 35, wherein administration of the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is continued about six months.

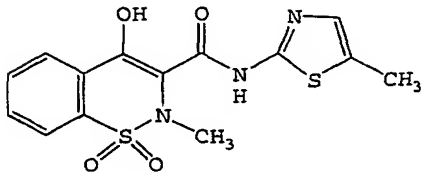
37. The method of claim 35, wherein administration of the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is continued for the life of the subject.

38. The method of claim 1, further comprising administration of a compound selected from the group consisting of an antithrombotic agent, a platelet aggregation inhibitor, and a combination thereof.

39. The method of claim 1, further comprising administration of at least one corticosteroid.

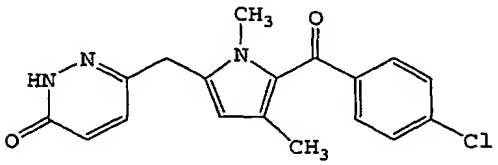
40. The method of claim 1, further comprising administration of at least one anti-inflammatory selected from the group consisting of sulfasalazine, griseofulvin, chochicine, curcumin, and tranilast.

41. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises:



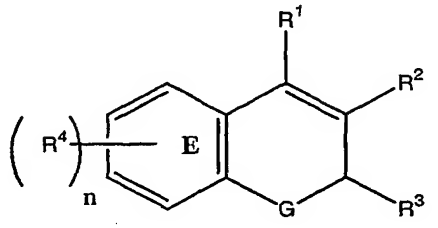
or pharmaceutically acceptable salt or prodrug thereof.

42. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises:



or a pharmaceutically acceptable salt or prodrug thereof.

43. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a compound of the formula:



(I)

wherein n is an integer which is 0, 1, 2, 3 or 4;

wherein G is O, S or NR^a;

wherein R^a is alkyl;

wherein R^1 is selected from the group consisting of H and aryl;

wherein R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

wherein R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical;

or a pharmaceutically acceptable salt or an isomer or a prodrug thereof.

44. The method of claim 43, wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or NR^b;

R^1 is H;

R^b is alkyl;

R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

each R^4 is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

45. The method of claim 43, wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is oxygen or sulfur;

R^1 is H;

R^2 is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

R^3 is lower haloalkyl, lower cycloalkyl or phenyl; and

each R^4 is H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or

wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

46. The method of claim 43, wherein:

R^2 is carboxyl;

R^3 is lower haloalkyl; and

each R^4 is H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

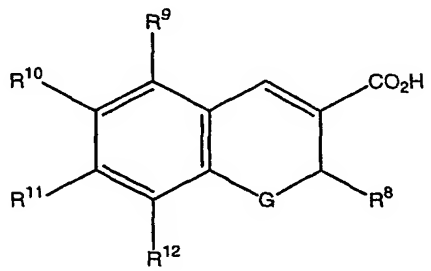
47. The method of claim 43, wherein:

n is an integer which is 0, 1, 2, 3 or 4;

R^3 is fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, or trifluoromethyl; and

each R^4 is H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

48. The method of claim 43, wherein the cyclooxygenase-2 selective inhibitor comprises a compound of the formula:



(Ia)

G is oxygen or sulfur;

R^8 is trifluoromethyl or pentafluoroethyl;

R^9 is H, chloro, or fluoro;

R^{10} is H, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, or morpholinosulfonyl;

R^{11} is H, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, or phenyl; and

R^{12} is H, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, or phenyl

49. The method of claim 43, wherein the cyclooxygenase-2 selective inhibitor, pharmaceutically acceptable salt, isomer or prodrug thereof is selected from the group consisting of:

6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

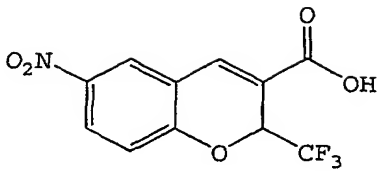
6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid; and

6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

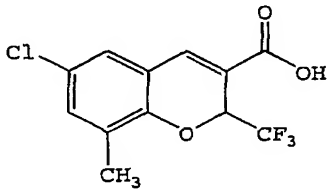
50. The method of claim 43, wherein the cyclooxygenase-2 selective inhibitor, pharmaceutically acceptable salt or prodrug thereof is selected from the group consisting of formulas:

a)



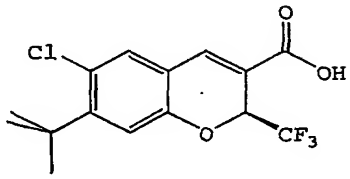
6-Nitro-2-trifluoromethyl-2H-1
-benzopyran-3-carboxylic acid

b)



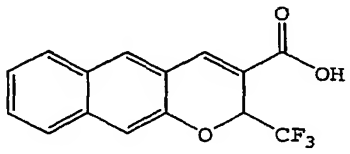
6-Chloro-8-methyl-2-trifluoromethyl
-2H-1-benzopyran-3-carboxylic acid

c)



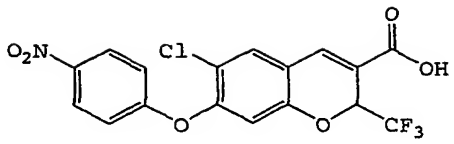
((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo
romethyl-2H-1-benzopyran-3-carboxylic acid

d)



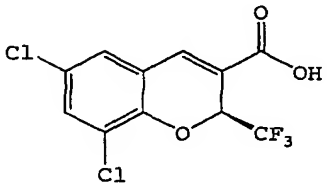
2-Trifluoromethyl-2H-naphtho[2,3-b]
pyran-3-carboxylic acid

e)



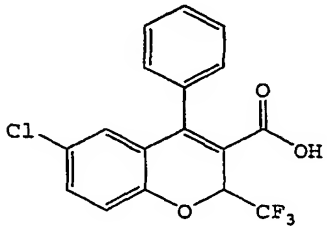
6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

f)



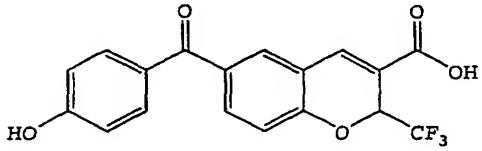
((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

g)



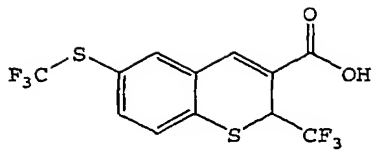
6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid

h)



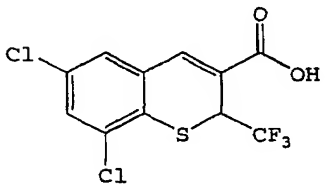
6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

i)



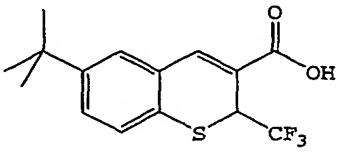
2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]
-2H-1-benzothiopyran-3-carboxylic acid

j)



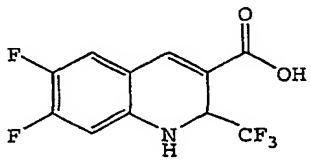
6,8-Dichloro-2-trifluoromethyl-2H-1-
benzothiopyran-3-carboxylic acid

k)



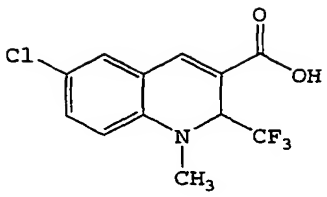
6-(1,1-Dimethylethyl)-2-(trifluoromethyl)
-2H-1-benzothiopyran-3-carboxylic acid

l)



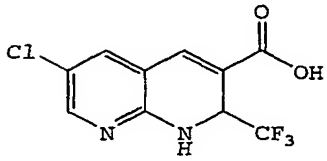
6,7-Difluoro-1,2-dihydro-2-(trifluoro
methyl)-3-quinolinecarboxylic acid

m)



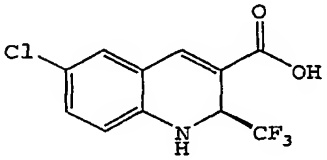
6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid

n)



6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid

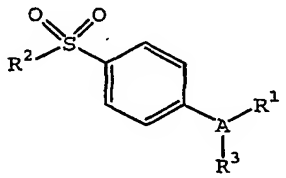
o)



((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

and any combination thereof.

51. The method of claim 1, wherein the cyclooxygenase inhibitor comprises a composition of the formula:



wherein A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R^1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

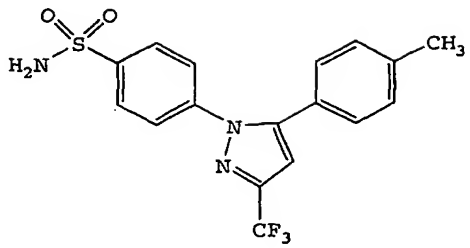
wherein R^2 is selected from the group consisting of methyl or amino; and

wherein R^3 is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

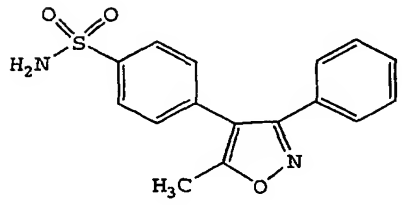
or a pharmaceutically acceptable salt or prodrug thereof.

52. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor pharmaceutically acceptable salt or prodrug thereof is selected from the group consisting of:

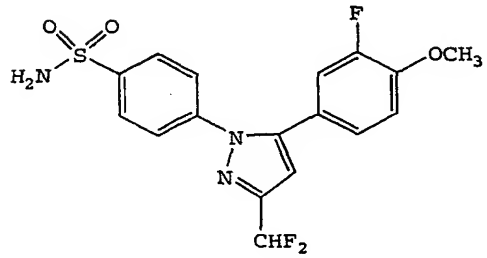
a)



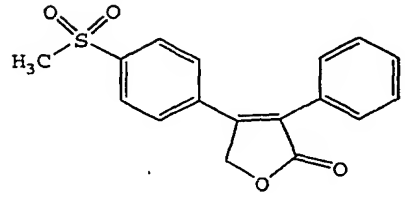
b)



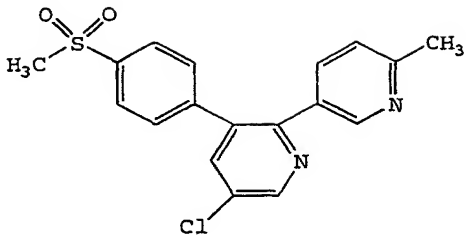
c)



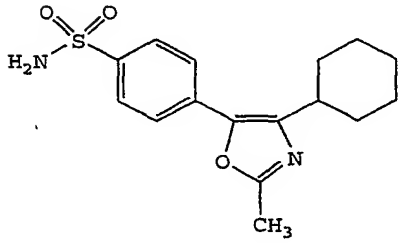
d)



e)



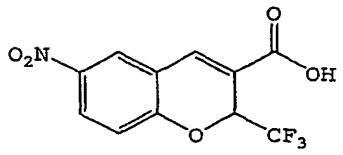
f)



and any combination thereof.

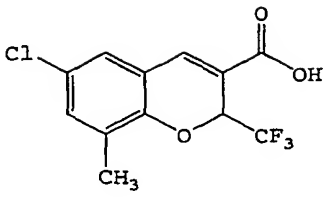
53. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof is selected from the group consisting of:

a)



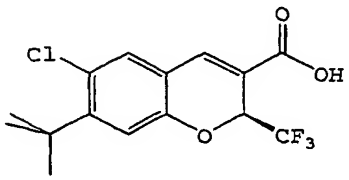
6-Nitro-2-trifluoromethyl-2H-1
-benzopyran-3-carboxylic acid

b)



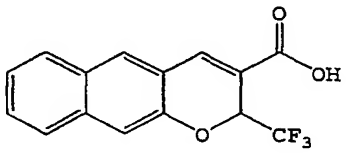
6-Chloro-8-methyl-2-trifluoromethyl
-2H-1-benzopyran-3-carboxylic acid

c)



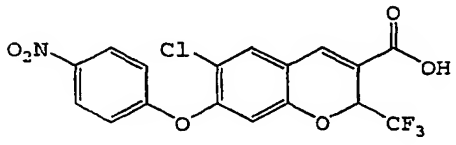
((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo
romethyl-2H-1-benzopyran-3-carboxylic acid

d)



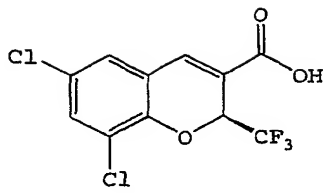
2-Trifluoromethyl-2H-naphtho[2,3-b]
pyran-3-carboxylic acid

e)



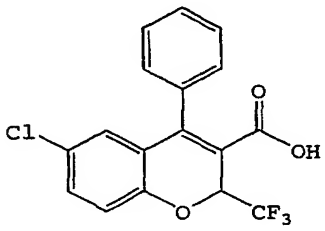
6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1
benzopyran-3-carboxylic acid

f)



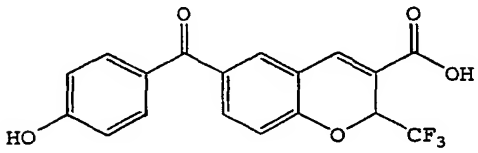
((S)-6,8-Dichloro-2-(trifluoromethyl)-
2H-1-benzopyran-3-carboxylic acid

g)



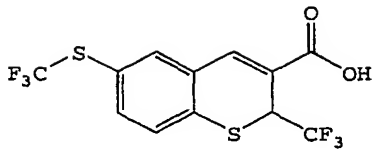
6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-
1-benzopyran-3-carboxylic acid

h)



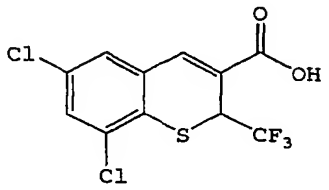
6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)
-2H-1-benzopyran-3-carboxylic acid

i)



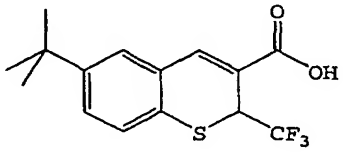
2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]
-2H-1-benzothiopyran-3-carboxylic acid

j)



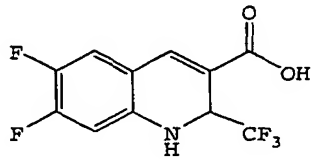
6,8-Dichloro-2-trifluoromethyl-2H-1-
benzothiopyran-3-carboxylic acid

k)



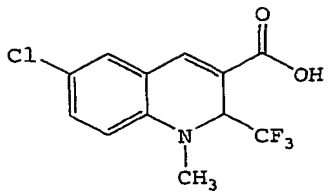
6-(1,1-Dimethylethyl)-2-(trifluoromethyl)
-2H-1-benzothiopyran-3-carboxylic acid

l)



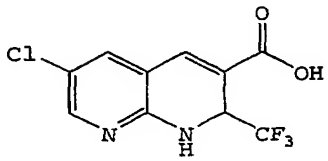
6,7-Difluoro-1,2-dihydro-2-(trifluoro
methyl)-3-quinolinecarboxylic acid

m)



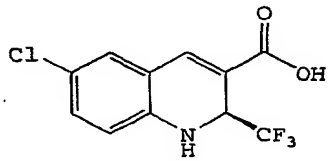
6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid

n)



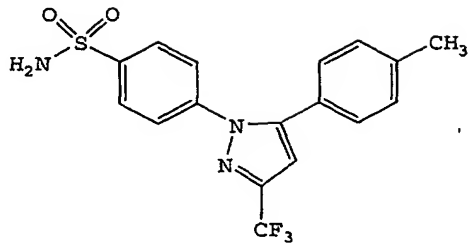
6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid

o)

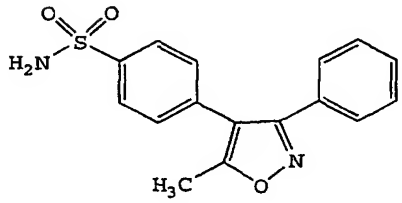


((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

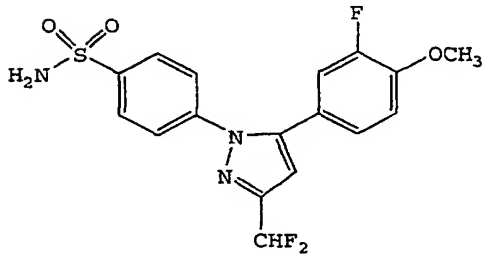
p)



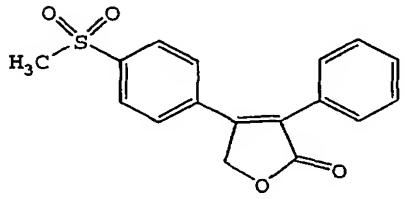
q)



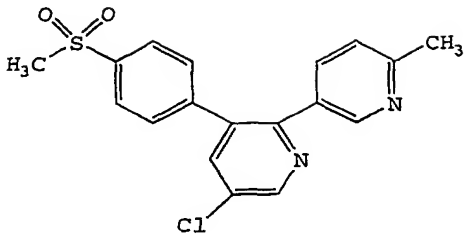
r)



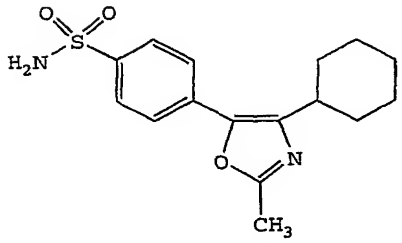
s)



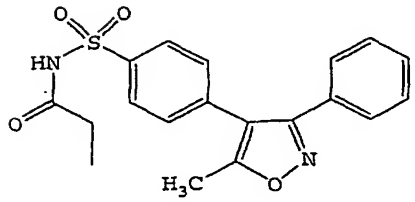
t)



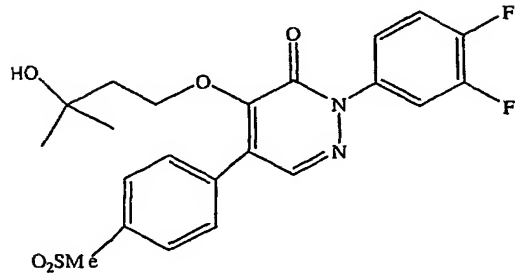
u)



v)

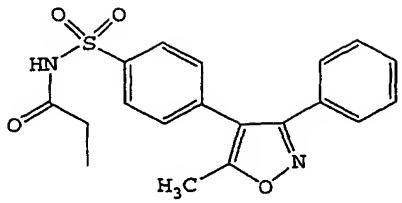


w)



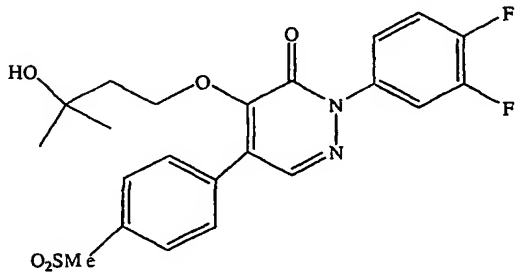
and any combination thereof.

54. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises:



or a pharmaceutically acceptable salt or prodrug thereof.

55. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises:



or a pharmaceutically acceptable salt or prodrug thereof.

56. The method of claim 1 wherein the cyclooxygenase–2 selective inhibitor comprises 4-[4-(methyl)-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone, or a pharmaceutically acceptable salt or prodrug thereof.

57. The method of claim 1 wherein the cyclooxygenase–2 selective inhibitor comprises, 4-(5-methyl-3-phenyl-4-isoxazolyl), or a pharmaceutically acceptable salt or prodrug thereof.

58. The method of claim 1 wherein the cyclooxygenase–2 selective inhibitor comprises, 2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine, or a pharmaceutically acceptable salt or prodrug thereof.

59. The method of claim 1 wherein the cyclooxygenase–2 selective inhibitor comprises, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl], or a pharmaceutically acceptable salt or prodrug thereof.

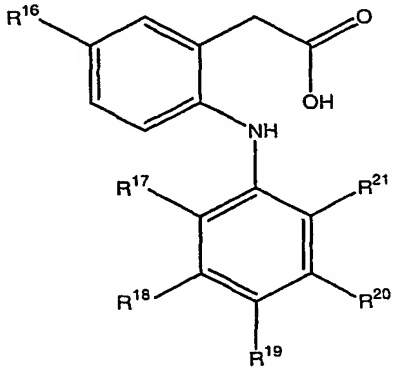
60. The method of claim 1 wherein the cyclooxygenase–2 selective inhibitor comprises, N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl], or a pharmaceutically acceptable salt or prodrug thereof.

61. The method of claim 1 wherein the cyclooxygenase–2 selective inhibitor comprises, 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, or a pharmaceutically acceptable salt or prodrug thereof.

62. The method of claim 1 wherein the cyclooxygenase–2 selective inhibitor comprises, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, or a pharmaceutically acceptable salt or prodrug thereof.

63. The method of claim 1, wherein the cyclooxygenase–2 selective inhibitor comprises, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridzainone, or a pharmaceutically acceptable salt or prodrug thereof.

64. The method of claim 1, wherein the cyclooxygenase–2 selective inhibitor comprises a compound of the formula:



(III)

wherein:

R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro;

R^{21} is chloro, fluoro, trifluoromethyl or methyl,

provided that R^{17}, R^{18}, R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H; or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

65. The method of claim 64, wherein:

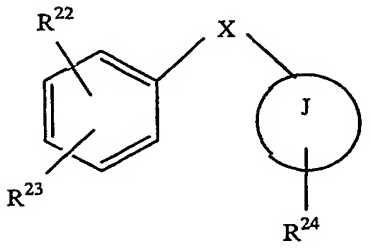
R^{16} is ethyl;

R^{17} and R^{19} are chloro;

R^{18} and R^{20} are hydrogen; and

and R^{21} is methyl.

66. The method of claim 1, wherein the cyclooxygenase–2 selective inhibitor comprises a compound of the formula:



(IV)

wherein:

X is O or S;

J is a carbocycle or a heterocycle;

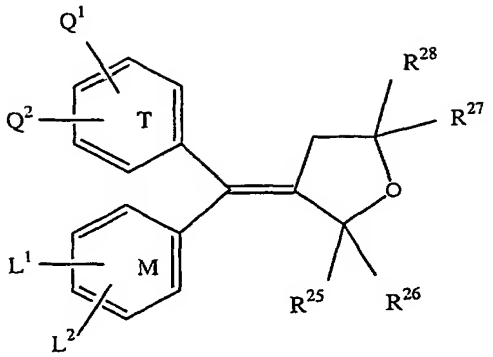
R^{22} is $NHSO_2CH_3$ or F;

R^{23} is H, NO_2, or F; and

R^{24} is H, $NHSO_2CH_3$, or $(SO_2CH_3)C_6H_4$;

or an isomer, a pharmaceutically acceptable salt, an ester, or a prodrug thereof.

67. The method of claim 1, wherein the cyclooxygenase–2 selective inhibitor comprises a compound of the formula:



(V)

wherein:

T and M independently are phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

Q^1, Q^2, L^1 or L^2 are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, or lower methoxy having from 1 to 6 carbon atoms; and

at least one of Q^1, Q^2, L^1 or L^2 is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or,

Q^1 and Q^2 are methylenedioxy; or

L^1 and L^2 are methylenedioxy; and

R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{25} and R^{26} are O; or,

R^{27} and R^{28} are O; or,

R^{25}, R^{26}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or,

R^{27}, R^{28}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer, a pharmaceutically acceptable salt, an ester, or a prodrug thereof.

68. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor or pharmaceutically acceptable salt or prodrug thereof comprises a chromene compound.

69. The method of claim 68, wherein the chromene compound is a benzopyran or substituted benzopyran analog.

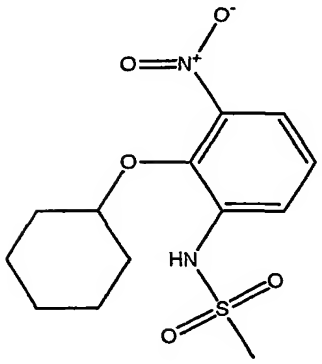
70. The method of claim 69, wherein the benzopyran or substituted benzopyran analog is selected from the group consisting of benzothiopyrans, dihydroquinolines and dihydronaphthalenes.

71. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor or pharmaceutically acceptable salt or prodrug thereof comprises a tricyclic compound.

72. The method of claim 71, wherein the tricyclic compound comprises a benzenesulfonamide or methylsulfonylbenzene.

73. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor or pharmaceutically acceptable salt or prodrug thereof comprises a phenyl acetic acid derivative.

74. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises:



B-26

or pharmaceutically acceptable salt or prodrug thereof.

75. The method of claim 1, wherein the cyclooxygenase-2 selective inhibitor, pharmaceutically acceptable salt, isomer, or prodrug thereof is selected from the group consisting of:

3-[(3-Chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one;

8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a);

5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone ;

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene ;

4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;
1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;
N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;
2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;
2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone;
6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
[2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid;
N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide;
N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide;
N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, soldium salt;
N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide;
3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one;
(5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4(5H)-thiazolone;
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide;

(6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid;

4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one;

6-dioxo-9H-purin-8-yl-cinnamic acid;

4-[4-(methyl)-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

4-(5-methyl-3-phenyl-4-isoxazolyl);

2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl];

N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl];

4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;

2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridzainone;

2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; and

[2-(2,4-dichloro-6-ethyl-3,5-dimethyl-phenylamino)-5-propyl-phenyl]-acetic acid .

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/17552

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N5/10 A61K31/00 A61K31/5415 A61K31/635 A61K31/42
A61K31/416 A61K31/341 A61K31/4418 A61K31/18 A61K31/501

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, BIOSIS, EPO-Internal, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 136 804 A (NICHTBERGER STEVEN A) 24 October 2000 (2000-10-24) Compounds 3,9,13 claims 1,4,14 column 4, line 23-27 column 14, line 38,39,45,46	1-75
X	US 6 077 850 A (DEVADAS BALEKUDRU ET AL) 20 June 2000 (2000-06-20) cited in the application column 6, line 25-39 column 24, line 43,44	1-75
X	US 5 616 601 A (GD SEARLE & CO) 1 April 1997 (1997-04-01) column 1, line 15-18 column 38, line 62,63	1-75

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 November 2002	21/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allnutt, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FITZGERALD G A; CHENG Y; AUSTIN S: "COX-2 inhibitors and the cardiovascular system" CLINICAL & EXPERIMENTAL RHEUMATOLOGY, vol. 19, no. 25, 2001, pages s31-s36, XP002218626 see abstract, lines 42-46 ---	1,5-38, 41-75
A	MILAS L ET AL: "ENHANCEMENT OF TUMOR RESPONSE TO GAMMA-RADIATION BY AN INHIBITOR OF CYCLOOXYGENASE-2 ENZYME" JOURNAL OF THE NATIONAL CANCER INSTITUTE, US DEPT. OF HEALTH, EDICATIONAND WELFARE, PUBLIC HEALTH, US, vol. 91, no. 17, September 1999 (1999-09), pages 1501-1504, XP000885785 ISSN: 0027-8874 page 1501, column 2, line 19-22 page 1503, column 2, line 10-15 ---	1-75
A	WO 00 38716 A (MASFERRER JAIME L ;SEARLE & CO (US); MCKEARN JOHN P (US); MILAS LU) 6 July 2000 (2000-07-06) See claims ---	1-75
P,X	TRIES S; LAUFER S; RADZIWON P; BREDDIN H K: "Antithrombotic and platelet function inhibiting effects of ML3000, a new antiinflammatory drug with COX/5-LOX inhibitory activity" INFLAMMATION RESEARCH, vol. 51, 2002, pages 129-134, XP002218627 column 1, line 11,12 page 2, column 1, line 15-17 -----	1-3, 5-38, 41-75

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/17552

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 1 and its dependent claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-75
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-75

Present claim 1 (and its dependent claims 1-75) relates to an extremely large number of possible diseases due to the term "cardiovascular disease" which is considered vague and unclear. Consequently, the search has been restricted to thrombosis, intimal hyperplasia and restenosis as defined in claim 2 and in the description (pg1, l. 8).
The disorder/disease "local inflammation" does not appear to be related to the above defined cardiovascular disorders, thus leading to a lack of clarity (Art 6 PCT).
Hence for this aspect, incomplete search for claims 1-75.

In claim 1, the expression "cyclooxygenase-2 selective inhibitor" is defined by reference to a desirable characteristic or property. This leads to a lack of clarity (Article 6 PCT) and is such as to render a meaningful search over the whole claimed scope impossible.
Consequently, a search has been carried out for those clear, supported and concise claims i.e. the compounds defined in claims 41, 42, 54, 74 and compounds disclosed in the description (16, l. 8 and 11; pg 26, l. 21-24; pg 28, l. 4-6; pg 29, l.5) namely meloxicam, celecoxib, valdecoxib, deracoxib, etoricoxib, parecoxib, valdecoxib and NS-398.
In addition, this term "cyclooxygenase-2 selective inhibitor" encompasses a very large number of possible compounds which may have this characteristic and a complete search is therefore not possible.
The applicants attention is drawn to the fact that some compounds may be already known to treat the diseases/disorders claimed by the applicant but are as yet not identified as cox-2 selective inhibitors.
Hence for this aspect, incomplete search for claims 1-40, 43-53, 55-73 and 75

Taken together, independent claims 43, 51, 52, 53, 55-63, 64, 66-71, 73 and 75 (and their dependent claims) cover an extremely large number of compounds leading to such a lack of conciseness (Article 6) that a meaningful search carried out over the whole claimed scope would be impossible.
Consequently, although specific compounds have been defined within the description, again there is a lack of conciseness. In addition, the search could not be limited to the examples since no specific compounds are defined, only 'cox-2 inhibitors'.
Therefore the search has been carried out for those claims which appear to be sufficiently supported by named compounds cited in the description as mentioned above.
Hence for this aspect, incomplete search for claims 43-53, 55-73 and 75.

The expression "dose of radiation" in claim 1 (including dependent claims 2-6, 12-15, 29-75) is considered to be so broad as to lead to a lack of clarity (Article 6 PCT) and is such as to render a meaningful search over the whole claimed scope impossible. For example, exposure to the sun and a television set may be covered by the radiation disclosed in claim 1.
In addition, claims 11-15 are considered to be unclear (Article 6) since the source of radiation cannot be determined and it is not sufficient to

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

define a radiation by its dose.
Consequently, the search has been restricted to those claims that appear to be clear, supported and concise i.e. claims 7-9, 16-28.
Hence for this aspect, incomplete search for claims 1-6, 12-75.

The term "negative remodeling" in claim 2 is unclear (Art 6 PCT) to such an extent that it is not considered to be an acceptable term and no further sufficient clarification is provided in the description.
Therefore no search was carried out for claim 2.

The terms "antithrombotic agent", "platelet aggregation inhibitor" in claim 38 are defined by reference to a desirable characteristic or property. This leads to a lack of clarity (Article 6 PCT) and is such as to render a meaningful search over the whole claimed scope impossible. Since there does not appear to be support in the description for claim 38, the search was carried out using these terms but the applicants attention is drawn to the fact that some compounds may already be known to treat the diseases/disorders claimed by the applicant in combination with cox-2 inhibitors but are as yet not identified as antithrombotic agent and platelet aggregation inhibitors.
Hence for this aspect, incomplete search for claims 38

The term "corticosteroid" in claim 39 relates to an extremely large number of possible compounds and is considered vague and unclear (Article 6). A complete search is therefore not possible. Consequently, the search has been limited to the compounds disclosed in the description on page 114, l. 9-10, namely hydrocortisone, dexamethasone and methylpridnisolnoe. The applicants attention is drawn to the fact that some compounds may be already known to treat the diseases/disorders claimed by the applicant in combination with cox-2 inhibitors but are as yet not identified as corticosteroids.
Mutatis Mutandis for claim 40, based on the term "anti-inflammatory", the search has been limited to the specific compounds claimed, namely sulfasalazine, griseofulvin, chochicine, curcumin and tranilast.
Hence for this aspect, incomplete search for claims 39 and 40.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/17552

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INTERNATIONAL SEARCH REPORT

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International Application No
PCT/US 02/17552

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF COMPOSITIONS COMPRISING CYCLOOXYGENASE-2 SELECTIVE INHIBITORS IN COMBINATION WITH RADIATION FOR INHIBITION OR PREVENTION OF CARDIOVASCULAR DISEASE

(57) Abstract: A method is provided for the prevention or inhibition of cardiovascular disease comprising the adminiministration of a cyclooxygenase-2 selective inhibitor with a dose of radiation.

WO 02/096516 A1